CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022408Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review of NDA Resubmission

PRODUCT (Generic Name):	Spinosad 0.9%
PRODUCT (Proposed Brand Name):	TRADENAME
NDA:	22-408
TYPE:	505(b)(1)
PROPOSED INDICATIONS:	pediculocide
SUBMISSION DATES:	7/23/10
SPONSOR:	ParaPro Pharmaceuticals
REVIEWER:	CAPT E. Dennis Bashaw, Pharm.D.
OCP DIVISION:	DCP III

Spinosad 0.9% is being developed for the control of human head lice (b) (4) An original NDA for this product was submitted in Jan. 2009 and a complete response letter was issued on Nov. 18th, 2009. Two issues presented in the letter dealt with the pharmacokinetics of benzyl alcohol (item 1 b) and dermal absorption in pediatric patients (item 2).

FDA CR LETTER ITEM 1

Item 1 FDA agrees that spinosad, containing spinosyns A and D in a ratio of approximately 5:1, is a single active ingredient. However, we have recently approved a product containing benzyl alcohol (present at 5%) as an active ingredient for the treatment of head lice. This would indicate that your product contains two active ingredients: spinosad and benzyl alcohol (b) (4)

A. Provide information to support approval of your product according to the regulations for fixed-combination prescription drugs at 21 CFR 300.50.

B. Provide pharmacokinetic data for benzyl alcohol in lice-infested subjects.

C. Submit complete CMC information on the drug substance, benzyl alcohol.

D. Submit complete nonclinical information to support the safety of benzyl alcohol per the ICH M3 (R2) guidance titled "Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals".

Sponsor's Response

For items #1 A thru #1D in the Agency's Complete Response Letter, we propose to rely on the existing clinical, pharmacokinetic, CMC, and nonclinical information to support the safety and efficacy of the ParaPRO product as a single active ingredient medication.

FDA Discussion

With regards to item 1b the sponsor has essentially elected to not respond, as in their opinion, there is no issue to respond to as they maintain benzyl alcohol is not an active ingredient, therefore, no need for additional or "any" pk data related to benzyl alcohol. The issue of whether or not benzyl alcohol is or is not an active ingredient is deferred to the Medical Reviewer.

FDA CR LETTER ITEM 2

Item 2 Although your maximal usage pharmacokinetic trials detected no systemic exposure of spinosad from the use of TRADENAME (spinosad) Suspension, 0.9%, only 8 healthy subjects under the age of 4 years were evaluated. The youngest subjects with head lice are at greatest risk for systemic exposure due to their greater surface-to-volume ratio and the effects of the infestation itself on the scalp.

(b) (4)

Sponsor's Response

The sponsor cites a "precedent" from the approval of the Ulesfia (NDA 22-129) application where the product received a pediatric indication for subjects 6 mos and older with a seemingly lesser amount of information.

> *"The recently approved head lice medication Ulesfia received a use claim for subjects 6 months and older and provided PK data for only 6 patients ranging in age from 6 to 36 months. ParaPRO exceeded that number by 33%, providing PK data on 8 subjects in an even younger age range from 6 to 23 months"*

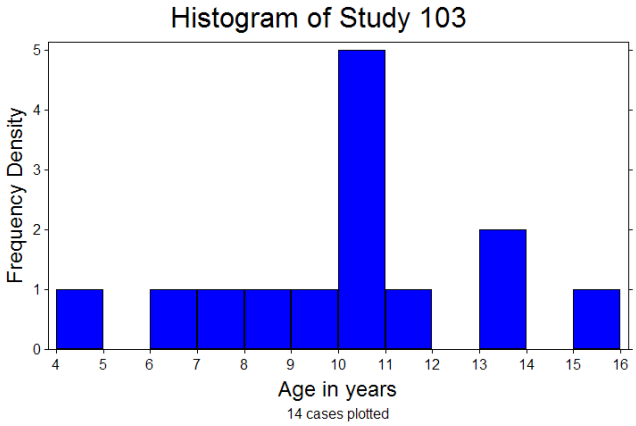
The sponsor goes on to state that they (b) (4) but that they are concerned with "a level playing field" for their product.

FDA Discussion

The FDA supports and strongly encourages a "level playing field" for sponsors. However, in doing so we must be cognizant that the primary difficulty in their comparision to the Ulesfia data is that in the Ulesifa NDA (as indicated in both the approved label and in the NDA reviews available on Drugs@FDA) the study was done in patients with lice infestation. We draw attention to the first paragraph of FDA's comment #2 where it is made quite clear that we are concerned not only with the small numbers but the lack of information in subjects with lice infestation. This comment then goes on to discuss our concerns in this area "*The youngest subjects with head lice are at*

greatest risk for systemic exposure due to their greater surface-to-volume ratio and the effects of the infestation itself on the scalp"

In comparison, the six subjects below the age of 2 cited in the Ulesfia dataset did have concomitant lice infestation. Thus, in fact, instead of "a level playing field" the sponsor is "mixing apples and oranges" or equating data in healthy subjects with those with lice infestation which does not represent "a level playing field" towards Ulesfia. The sponsor did conduct a trial in children with lice infestation, but the cut-off in that study was 4yrs of age (see below).



In fact, our acceptance of this data with regards to the proposed 4 yr cut-off is consistent with our acceptance of the limited data cited with Ulesfia in the younger age range. The difference here is the fact that the Ulesfia data, again, was in patients and not healthy subjects.

Conclusion

CR Letter Item 1

The issue of whether or not benzyl alcohol is or is not an active ingredient is deferred to the Medical Reviewer. Should it be decided that it is an active ingredient, then the Division of Clinical Pharmacology will provide input as to the type of study needed to address item 1b of this comment.

CR Letter Item 2

The sponsors proposal (b) (4) is unacceptable. The issue cited in the CR letter was related to the lack of in vivo pk data in subjects with active lice infestation below the age of 4yrs. The data cited by the sponsor vis a vis the Ulesfia approval overlooks the fact that the Ulesfia data was collected in subjects with an active infestation. This point is clearly indicated in the current Ulesfia package insert. The Division of Clinical Pharmacology has maintained that for topically applied products, bioavailability testing must be accomplished in subjects with the disease of interest as normal skin is a poor surrogate for diseased skin and is not accepted as such by the Division and Office of Clinical Pharmacology.

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/s/

EDWARD D BASHAW
10/06/2010

Filing Review
Spinosad (b) (4)
NDA 22-408
Reviewer: E.D. Bashaw, Pharm.D.

CLINICAL PHARMACOLOGY OVERVIEW

The Clinical Program for the development of SPINOSAID included three Phase 1 studies that evaluated pharmacokinetics (PK). Of these studies only SPN-106-06 used (b) (4) 1.0%, the other two studies, including the only study in subjects with head lice, used the 2% product, the studies are briefly summarized below.

Healthy Subjects

Study SPN-101-04 was a Phase 1, open-label, single-center study conducted over a period of seven days to determine the PK profile of spinosad 2.0% after a single treatment application. Twenty-three (23) healthy volunteers, 21 – 60 years of age, were enrolled into the study and applied spinosad 2.0% to their scalps for 10 minutes.

Study SPN-106-06 was a Phase 1, open-label, single-center study conducted over a period of two days to determine the PK profile of a single treatment of spinosad 1.0% (NatrOVA). Eight (8) healthy pediatric subjects, 6 – 23 months of age, were enrolled. The study consisted of two visits; subjects remained in the clinic during the second visit, which included a 4-hour, post-application blood draw. In this study, all subjects were treated with a single topical (scalp) application of spinosad 1.0% for 10 minutes, after which the treatment was washed off, and subjects underwent PK evaluations.

Subjects with Head Lice

Study SPN-103-05 was a Phase 1, open-label, single-center study conducted over a period of seven days to determine the PK profile of spinosad 2.0% in pediatric subjects with *P. capitis*. Fourteen (14) subjects, 4 – 15 years of age, with head lice were enrolled into the study. All subjects applied a single topical (scalp) treatment of spinosad 2.0% for 10 minutes, after which the test article was washed off, and subjects underwent PK evaluations.

The PK evaluation for the studies included assessments of spinosyn A and spinosyn D plasma concentration levels over time and a derivation of parameters that included AUC0-t, Cmax, and Tmax.

Results

Overall, in each study, all collected samples were below the limits of quantification (BLQ) (< 3 ng/mL) and thus, no analyses of spinosad and/or spinosad metabolite concentrations could be made. From this the sponsor has concluded that a 10-minute topical applications of spinosad 1.0% (NatrOVA) and spinosad 2.0% did not result in any systemic absorption by healthy adult subjects (SPN-101-04 spinosad 2.0%), healthy pediatric subjects (SPN-106-06 spinosad 1.0%), or pediatric subjects with head lice (SPN-103-05 spinosad 2.0%).

RECOMMENDATION-Fileable

Ideally it would have been nice had they used the spinosad 1.0% product all throughout the program, but with the finding of no absorption with the spinosad 2.0% product under conditions of use, I have no objections and the application appears to be fileable from a Clin Pharm perspective.

Target Review Completion Date-June 15th

74 Day Letter Comments-None

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/s/

EDWARD D BASHAW
10/06/2009

Clinical Pharmacology Review

PRODUCT (Generic Name):	Spinosad 0.9%
PRODUCT (Proposed Brand Name):	TRADENAME
NDA:	22-408
TYPE:	505(b)(1)
PROPOSED INDICATIONS:	pediculocide
SUBMISSION DATES:	1/21/09
SPONSOR:	ParaPro Pharmaceuticals
REVIEWER:	CAPT E. Dennis Bashaw, Pharm.D.
OCP DIVISION:	DCP III

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

TRADENAME (spinosad 0.9%) is being developed for the control of human head lice (b) (4) Spinosad belongs to a class of insecticides derived from the fermentation process of a naturally occurring soil actinobacterium, *Saccharopolyspora spinosa* and has been used successfully as an insecticide against a large number of crop and garden pests, reportedly with minimal effects on beneficial insects. More recently, research has focused on the use of spinosad in the treatment of chewing and sucking lice infestations on dairy and beef cattle, as well as on sheep. According to the sponsor, spinosad demonstrates low toxicity effects in humans, other mammals, and birds and it is metabolized into simple, organic compounds.

The clinical program for the development of TRADENAME included six Phase 1 studies (three pharmacokinetic/tolerability, one cumulative irritation/skin sensitization, one photo-toxicity, and one photo-allergy), three Phase 2 studies (two dose-ranging and one pilot), and two Phase 3 studies (both pivotal, "actual use", safety and efficacy). In toto, 6 studies support the safety and 5 studies support both the safety and efficacy of TRADENAME in the treatment of *P. capitis*.

In each of the three Phase 1 studies, all samples collected were below the limits of quantification (< 3 ng/mL) and thus, no analyses of spinosad and/or spinosad metabolite concentrations could be made.

1.1 Recommendations

From a Clinical Pharmacology standpoint, the sponsor has met the requirements under 21 CFR 320 and the application is generally acceptable. That being said there is a lack of any pk data in lice infested subjects below the age of 4yrs. Considering that lice infestation is accompanied by scalp inflammation and bleeding (associated with lice feeding), we recommend that if the application was to be approved on this cycle that the lower age limit be (b) (4) 4yrs.

However, as the application will receive a C/R due to manufacturing "problems the Medical Officer has concluded in their review that additional clinical data is necessary for approval of this product (b) (4). Given this opportunity additional pk data in the younger age group can be obtained as part of the development program.

1.2 PMC/PMR

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Finding

The Clinical Program for the development of TRADENAME included three pharmacokinetic studies that used a 1.8% spinosad product, not the 0.9% product proposed for marketing. In study SPN-101-04, conducted in normal healthy subjects, blood samples were drawn pre-application (Hour 0) and post-application at 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours, and at Day 7. Study SPN-106-06, also conducted in normal healthy subjects, samples were drawn pre-application and at 1 and 4 hours post-application. Only study SPN-103-05 of the pk studies was conducted in subjects with lice infestation. In it samples were drawn pre-application (Hour 0) and post-application at 1, 2, 4, and 8 hours, and at Day 7. However, in that study, there are only 3 subjects below the age of 8 and no subjects below the age of 4yrs of age. Overall, the results from all 3 studies were the same, no systemic blood levels were detected in vivo. Given that the planned application time is 10 minutes, little time would be available for systemic absorption to occur prior to rinsing the product out of the hair. While the concentration used was not the to-be-marketed strength, as it was a higher concentration in the same vehicle, we can accept these findings as related and relevant.

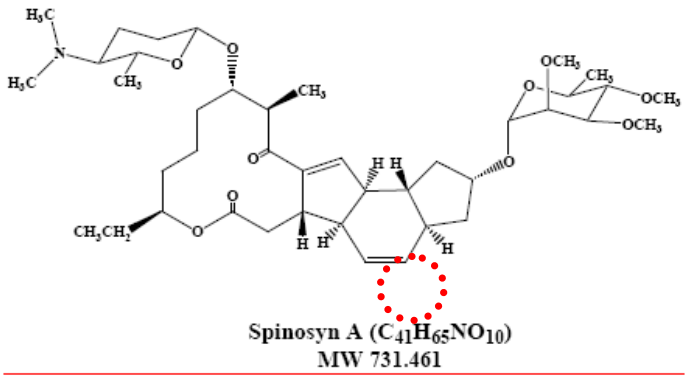
2 QUESTION BASED REVIEW

2.1 General Attributes

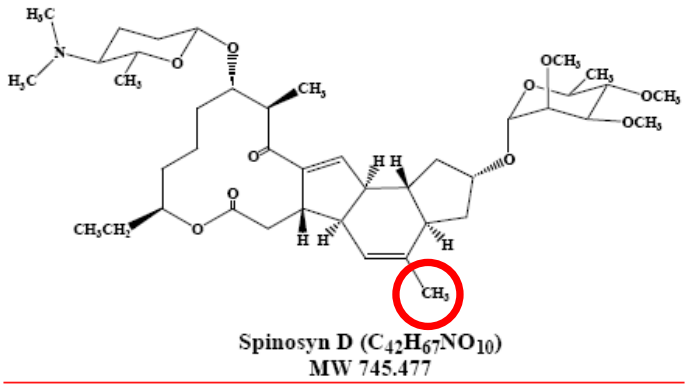
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product

Drug Substance and Formulation

Spinosad belongs to a class of insecticides derived from the fermentation process of a naturally occurring soil actinobacterium, *Saccharopolyspora spinosa* and has been used successfully as an insecticide against a large number of crop and garden pests. As a product of fermentation it exists as two different forms spinosad A and spinosad D:



Spinosyn A ($C_{41}H_{65}NO_{10}$)
MW 731.461



Spinosyn D ($C_{42}H_{67}NO_{10}$)
MW 745.477

Spinosyn A: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,a5-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16btetradecahydro-14-metyl-,(2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-

Spinosyn D: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,a5-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16btetradecahydro-4,14-dimetyl-,(2S,3aSR,5aS,5bS,9S,13S,14R,16aS,16bS)-

In the May 17, 2007 FDA Fax communication to the sponsor, The Agency recognized the combination of spinosyn A + D as a single active ingredient “spinosad”.

"Agency agrees to recognize spinosad as a single active ingredient in the sponsor's product (TRADENAME (b) (4). Spinosad is a naturally derived fermentation product composed of a mixture of related compounds containing primarily spinosyn A and D at a ratio of approximately 5:1. If spinosad is the only active ingredient in the product, then the fixed combination drug regulations in 21 CFR 300.50 will not apply."

Spinosad is completely (b) (4) for topical application on lice infested scalps. Of interest is the fact that the proposed product contains (b) (4) Benzyl Alcohol. The FDA has recently recognized benzyl alcohol alone as an effective pediculicide in its own right.

Test Formulas-0.5, 1.0, 2.0%

INCI Name	Trade Name	Source	CAS Number	FDA Inactive Use in Approved Drug Products (Topicals)	FDA Excipient Database Number of Citations (Topicals)	Target Conc % (w/w)	Purpose
Benzyl Alcohol	Benzyl Alcohol	NF	000100516	1-50%	85 (13)	(b) (4)	
Butylated hydroxytoluene	BHT	NF	000128370	0.05-2%	29 (10)		
Ceteareth-20	(b) (4)	CTFA	067762270	10%	5 (5)		
Cetearyl alcohol		NF	068439496	1.2-8%	12 (8)		
FD&C Yellow #6	FD&C Yellow No. 6, (b) (4) (b) (4)	FD&C	002783940	0.0016%	33 (3)		
Hexylene Glycol	Hexylene Glycol	NF	000107415	0.3-12%	4 (4)		
Hydrochloric Acid	(b) (4)	NF	7647010	NA	ND		
Hydroxethyl cellulose		NF	009004620	0.75-0.80%	25 (12)		
Isopropyl Alcohol	Isopropyl Alcohol	USP	000067630	4-99.5%	23 (10)		
Propylene Glycol	Propylene Glycol	USP	000057556	2-98%	102 (32)		
Sodium Hydroxide	Sodium Hydroxide	USP/NF		NA	ND		
Spinosad	Spinosad	NA	131929607 131929630	NA	NA	0.5-2%	Active ingredient
Stearalkonium chloride	Ammonyx4 (18%)	CTFA	000122190	3.5%	5 (4)	(b) (4)	
Water, (b) (4)							

According to information submitted in the chemistry portion of this application, isopropyl alcohol and benzyl alcohol were included in the formulation (b) (4) of spinosad. Given the timing of the different applications it is unlikely that this sponsor was aware of the pending application for the benzyl alcohol only product.

As shown in the formulation table above, the products in the NDA program were formulated to contain 0.5%, 1.0% and 2.0% total spinosyns (see *analytical summary* in Appendix). Due to a change in the way the Agency asked the sponsor to allow for other "related" spinosyns in the product their strengths were revised to result in a label claim (b) (4) as spinosyn (A+D) respectively. Ultimately the sponsor elected to pursue the 0.9% product for marketing. This is of some relevance as the 1.8% product was used in the clinical pharmacology studies. As it represents a higher concentration than what is proposed for marketing (and no blood levels were detected, in vivo) this is acceptable.

In terms of its structural makeup, the formulation was intended to provide a level of cosmetic "elegance" similar to marketed hair crème rinses to facilitate easy use, allow an easier comb out by detangling the hair, and enhance compliance with the total treatment. In a departure from most of the commonly used head lice products, TRADENAME will be marketed (b) (4) This is based on the sponsor's evaluation of their clinical program that the efficacy of TRADENAME in human clinical trials (b) (4)

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

In published studies to determine the mode of action of the spinosyns as an insecticide it was found to directly excite the insect nervous system, initially causing involuntary tremors and muscle contractions by acting on the neurons in the CNS. The excitation of the insect nervous system is considered to be due to persistent activation of nicotinic acetylcholine receptors and gamma-butyric acid gated ion channels in the insect's neurons. Thus it works through a mechanism of action similar to that of nerve gas.

In relation to *P. capitis*, spinosad has demonstrated efficacy against human louse eggs at all stages of development. Significantly, spinosad has been shown to be highly effective in killing permethrin-resistant head lice (a growing problem in the United States) and is equally effective against permethrin-sensitive body lice (*Pediculosis corporis*). These results suggest a lack of cross-resistance between the two treatments and indicate that susceptibility of human lice to spinosad is independent of permethrin resistance

2.1.3 What are the proposed dosage and route of administration?

The product is designed to be applied directly to dry hair for a period of 10 minutes. The amount of applied varies in direct proportion to the length of the hair. A sufficient amount should be applied to coat the entire hair shaft. The labeling provides the following guidance as to amount:

- Completely cover the scalp with TRADENAME first, and then apply to the hair working away from the scalp towards the ends of the hair.

- People with short to medium length hair (above the shoulder) may not need the entire 120 mL bottle to adequately cover the scalp and hair.

- For people with thick, medium length hair and people with long hair, up to 120 mL may be required to adequately cover the scalp and hair.

Following the 10 minute application time, the hair should be rinsed thoroughly with warm water. After rinsing, shampoo or other hair care products may be used. Should re-treatment be necessary, the same directions are to be followed.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Clinical Program for the development of TRADENAME included six Phase 1 studies (three pharmacokinetic/tolerability, one cumulative irritation/skin sensitization, one photo-toxicity, and one photo-allergy), three Phase 2 studies (two dose-ranging and one pilot), and two Phase 3 studies (both pivotal, "actual use", safety and efficacy). In toto, 6 studies support the safety and 5 studies support both the safety and efficacy of TRADENAME in the treatment of *P. capitis*.

The Phase 3 studies, SPN-301-07 and SPN-302-07 were designed identically and conducted simultaneously at different sites with different investigators and subjects. Both studies were multi-center, randomized, evaluator/investigator-blinded, parallel group, active-controlled trials designed to evaluate the safety and demonstrate the efficacy of TRADENAME relative to NIX under "actual use" conditions in subjects who were infested with *P. capitis* with the following key endnoints:

> Primary Endpoint
> Proportion of primary subjects in the enrolled households who were lice free (no live lice, adults or nymphs), as assessed by the trained evaluator, 14 days after the last treatment (i.e., Day 14 for subjects who treated once and Day 21 for subjects who treated twice).
>
> Secondary endpoint
> Proportion within each treatment group of all enrolled subjects (primary plus non-primary) in the households requiring two treatments.

A total of 1,038 subjects from 391 households were enrolled. Eligible subjects included males and females of any race/ethnicity within a household who were six months of age or older and presented with active cases of head lice. The mean age of all subjects (primary and non-primary ITT populations combined) ranged from 16 years (in SPN-302-07) to 17 years (in SPN-301-07). The primary subject in a household was the youngest individual in the household who had 3 live lice on examination who otherwise met the inclusion/exclusion criteria. Secondary subjects were defined as all other household members who met the inclusion/exclusion criteria (i.e., 1 live louse on examination). The majority of the subjects were female (82.5%) and Caucasian (59.6%), although substantial proportions also were Hispanic (36.5%). While African-American subjects were greatly under-represented in the studies, compared to their proportions in

the US population, race in general is not a susceptibility factor for head lice. The results of the two phase 3 and three pk studies are summarized below:

Pivotal Phase 3 Study #1: SPN-301-07

As noted above, both of the phase 3 trials used identical trial designs and endpoints. Across the study, 203 households—including 558 subjects—were enrolled.

Study 301 Success Rates

	Enrolled		Primary Subjects Only	All Subjects	
	Households	Subjects	1 Treatment		2 Treatments
TRADENAME with nit combing	23	59	19 (82.6%)	31 (88.6%)	22 (91.7%)
TRADENAME without nit combing	91	243	77(84.6%)	146 (94.2%)	49 (55.7%)
NIX	89	256	40 (44.9%)	62 (68.1%)	55 (33.3%)

As shown in the table above, of the enrolled primary subjects, 82.6%, 84.6% and 44.9% were considered successes in the TRADENAME with nit combing, TRADENAME without nit combing, and NIX treatment groups, respectively. The difference between the TRADENAME without nit combing and NIX treatment groups was statistically significant ($p<0.001$).

The secondary efficacy endpoint was the proportion within each treatment group of all enrolled subjects (primary and non-primary combined) who required two applications of study medication. Overall, the majority of subjects in the TRADENAME treatment groups (59.3% with and 63.8% without nit combing) required only one application of treatment, while the majority of subjects in the NIX treatment group (64.5%) required two. These results support the primary efficacy analysis.

Pivotal Phase 3 Study #2: SPN-302-07

Across the study, 188 households—including 480 subjects—were enrolled

Study 302 Success Rates

	Enrolled		Primary Subjects Only	All Subjects	
	Households	Subjects	1 Treatment		2 Treatments
TRADENAME with nit combing	21	63	17 (81%)	44 (86.3)	8(66.7%)
TRADENAME without nit combing	83	203	72 (86%)	163 (93.1%)	18 (64.3%)
NIX	84	214	36 (42.9%)	53 (62.4%)	35 (27.1%)

As shown in the table above, of the enrolled primary subjects, 81.0%, 86.7% and 42.9% were considered successes in the TRADENAME with nit combing, TRADENAME without nit combing, and NIX treatment groups, respectively. The difference between the TRADENAME without nit combing and NIX treatment groups was statistically significant

($p<0.001$) with estimated success rates for TRADENAME and NIX to be 89.1% and 45.1%, respectively.

The secondary efficacy endpoint was the proportion within each treatment group of all enrolled subjects (primary and non-primary combined) who required two applications of study medication. Overall, the majority of subjects in the TRADENAME treatment groups (81.0% with and 86.2% without nit combing) required only one application of treatment, while the majority of subjects in the NIX treatment group (60.3%) required two. These results support the primary efficacy analysis.

PK Study SPN-101-04

Phase 1, open-label, single-center study conducted over a period of seven days to determine the PK profile of spinosad 1.8% after a single treatment application. Twenty-three (23) *healthy volunteers*, 21 – 60 years of age, were enrolled into the study and applied spinosad 1.8% to their scalps for 10 minutes. The study consisted of screening and six study visits (Days 1 – 5 and 7). Blood was collected for analyses at time points that included: pre-application; 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours post-application; and Day 7. The PK evaluations included assessments of spinosyn A and spinosyn D plasma concentration levels over time and a derivation of PK parameters that included AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, and CL/F.

PK Study SPN-103-05 (PEDIATRIC POPULATION w/Lice Infestation)

Phase 1, open-label, single-center study conducted over a period of seven days to determine the PK profile of spinosad 1.8% in *pediatric subjects with P. capitis*. Fourteen (14) subjects, 4 – 15 years of age, with head lice were enrolled into the study. All subjects applied a single topical (scalp) treatment of spinosad 1.8% for 10 minutes, after which the test article was washed off, and subjects underwent PK evaluations. The study consisted of three visits; subjects remained in the clinic during the second visit, which included an 8-hour post-application blood draw and evaluation. Blood was collected for analyses at time points that included: Pre-application; 1, 2, 4, and 8 hours post-application; and Day 7. Subjects and/or their guardians were queried regarding AEs at all visits and at each assessment time point. The PK evaluation included an assessment of spinosyn A and spinosyn D plasma concentration levels over time and a derivation of PK parameters that included AUC0-t, Cmax, and Tmax.

PK Study SPN-106-06 (PEDIATRIC POPULATION)

Phase 1, open-label, single-center study conducted over a period of two days to determine the PK profile of a single treatment of spinosad 1.0% (TRADENAME). Eight (8) healthy pediatric subjects, 6 – 23 months of age, were enrolled. The study consisted of two visits; subjects remained in the clinic during the second visit, which included a 4-hour, post-application blood draw. In this study, all subjects were treated with a single topical (scalp) application of spinosad 1.0% for 10 minutes, after which the treatment was washed off, and subjects underwent PK evaluations. Blood was collected for analyses at time points that included pre-application, as well as 1 and 4 hours post-application. The PK evaluation included assessments of spinosyn A and spinosyn D plasma concentration levels over time and a derivation of parameters that included AUC0-t, Cmax, and Tmax.

Table 2.7.2.2-1: Summary of Pharmacokinetic Evaluations in the Phase 1 Studies

Study	Number of Samples (%)	Spinosad/Spinosad Metabolite Concentration
SPN-101-04	614 (100.0%)	BLQ[a]
SPN-103-05	136 (100.0%)	BLQ[a]
SPN-106-06	48 (100.0%)	BLQ[a]

[a] Below Limits of Quantification, i.e., <3 ng/mL

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, however, given that the two active species (spinosad A and D) were not detectable in the plasma it is not possible either assess pharmacokinetic parameters and exposure response relationships for spinosad.

2.2.3 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint was the proportion within each treatment group of primary subjects within the households who are lice free (without live lice) as assessed by a trained evaluator 14 days after the last treatment (i.e., Day 14 for subjects who treated once and Day 21 for subjects who treated twice). The secondary efficacy endpoint is the proportion within each treatment group of individual household members requiring two treatments. These endpoints were agreed on with the FDA and are typical of lice treatment protocols.

2.2.4 Exposure-Response

N/A

2.2.4.1 Does this drug prolong the QT or QTc interval?

To address this need a consult was sent to the FDA QT-IRT with the following question:

> *"Does cardiology agree that spinosad* (b) (4) *(TRADENAME) does not need electrocardigraphic evaluation such as a thorough QT/QTc study? It should be noted that the lack of evidence of systemic exposure in humans does not prove that the product is not absorbed in humans. However, for spinosad* (b) (4) *(TRADENAME), systemic exposure appears not to be detectable down to low levels, (< 3 ng/mL), the product is to be applied for a short period of time (10 minutes), and the treatment course is limited (one or two treatments per episode of head lice)."*

In a review by Christine Garnet, Ph.D. the QT-IRT responded:

"If you concur with the sponsor's assertion that there is no systemic exposure to spinosad and its metabolites at the clinically relevant doses, a TQT study is not needed for this product. According to the ICH E14 guideline, recommendations for a TQT study apply to new drugs having systemic bioavailability (see section I.B of ICH E14 guideline)."

The DDDP has determined that the absorption is low and undetectable; this coupled with the short contact time was their basis for not requiring a TQT study. We concur.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose (SD) and multiple dose (MD) PK parameters?

The drug is intended for single use only with retreatment in cases of treatment failure. Given that plasma levels are undetectable given the current route and method of administration, this element is not applicable.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The dermal absorption of a topical product is dependent upon the interplay of drug substance, formulation, and disease state. Given this, dermal absorption in normal volunteers is a poor predictor of absorption in diseased skin and it thus not relevant as one of the hallmarks of a lice infestation is itching and inflammation of the scalp that can lead to bleeding.

2.2.5.3 What are the characteristics of drug absorption?

While systemic availability in vivo cannot be determined, the sponsor did provide the following study report which considers in vitro drug penetration of stratum corneum.

Study 3787 This study was conducted in human cadaver skin with the formulated product used in clinical testing in humans, to determine if the formulation altered the penetration of the spinosyns through cadaver skin. The concentrations of spinosad in the formulation were 0.5%, 1.0%, and 1.8% w/v. After exposure to the skin for 24 hours, the mean total absorption as a percentage of the applied dose in all skin layers and receptor fluid was 15.8%. Of this, 6.6% was in the upper corneal layer, 2.9% in the lower stratum corneum, 6.2% in the epidermal/dermal skin, and 0.02% in the receptor fluid, the latter representing the absorbed compound. In other studies where the same formulation was washed off after 1 hour exposure to the skin, the mean total absorption as a percentage of the applied dose in all skin layers and receptor fluid was 1.4%. Of this, 0.6% was in the upper corneal layer, 0.3% in the lower stratum corneum, 0.5% in the epidermal/dermal skin, and 0.03% in the receptor fluid.

Amount of Spinosads Absorbed *in vitro* - Leave-on Modeling

	Total Absorption (% of Applied Dose)	mg Spinosads / 0.64cm^2 tissue	mg Spinosads / cm^2
mean	16.04%	0.0642	0.1003
std.dev.	5.71%	0.0228	0.0357

Amount of Spinosads Absorbed *in vitro* - Wash-off Modeling

	Total Absorption (% of Applied Dose)	mg Spinosads / 0.64cm^2 tissue	mg Spinosads / cm^2
mean	1.44%	0.0058	0.0090
std.dev.	0.59%	0.0024	0.0037

The unstated but implied conclusion is that if dermal permeation following 24hrs of contact was <<1.0% in the receptor fluid, then absorption in vivo following a 10min. exposure should not be of any concern. While this is speculative, it is to some degree re-assuring, in combination with the in vivo pk data we do have in hand.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Clinical Studies (Efficacy and Safety)

As has been noted previously, in the study summary, Eligible subjects included males and females of any race/ethnicity within a household who were six months of age or older and presented with active cases of head lice. A total of 1,038 subjects from 391 households were enrolled. The mean age of all subjects (primary and non-primary ITT populations combined) ranged from 16 years (in SPN-302-07) to 17 years (in SPN-301-07). The majority of the subjects were female (82.5%) and Caucasian (59.6%), although substantial proportions also were Hispanic (36.5%). While African-American subjects were greatly under-represented in the studies, compared to their proportions in the US population, race in general is not a susceptibility factor for head lice.

Study 301 Demographics

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

Study 302 Demographics

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

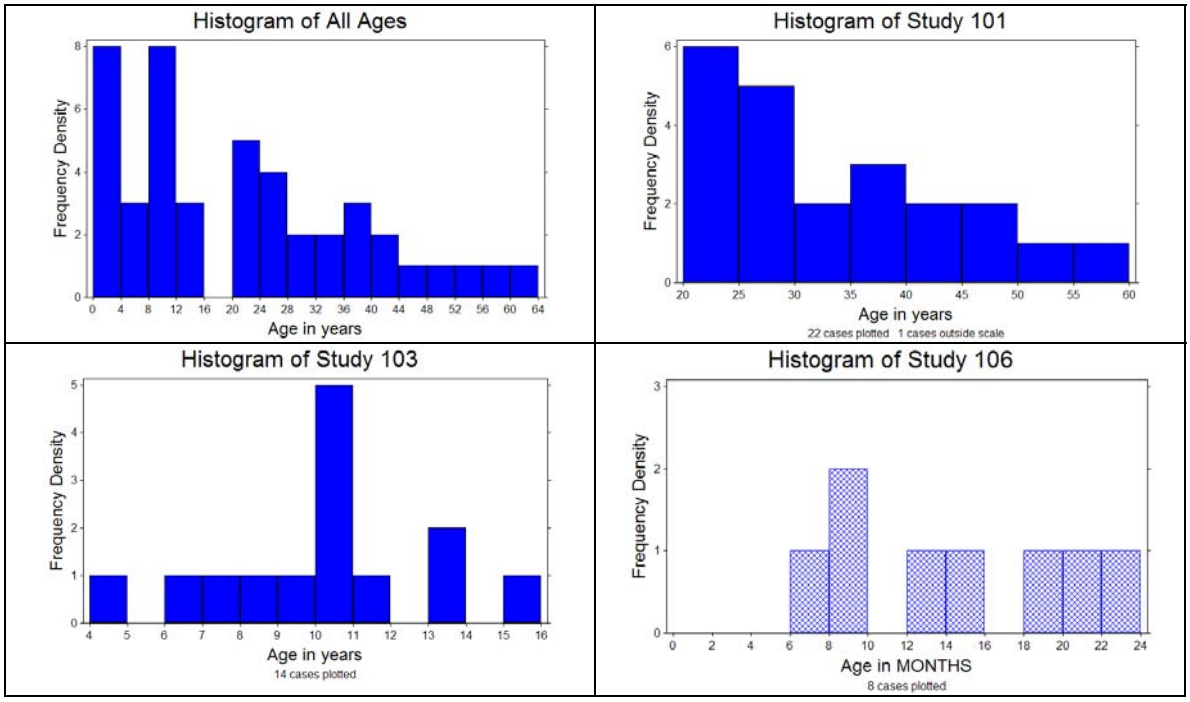
No differences in the response rate were identified relative to the demographic characteristics of the subjects.

Clin Pharm Studies (Studies 101, 103, and 106)

The only intrinsic factor that we have to consider in this population, related to exposure, is the age distribution of the subjects and the number of subjects in the clin pharm studies that had actual lice infestation. This latter point is important as a hallmark of active lice infestation is inflammation of the scalp related the feeding of the lice on blood. A summary of the clin pharm studies demographic information is presented below:

	Age	Study101	Study103	Study106
N	45	23	14	8
Mean	20.789	34.348	9.7143	1.1875
SD	16.685	11.907	2.8937	0.5175
Variance	278.39	141.78	8.3736	0.2678
SE Mean	2.4873	2.4828	0.7734	0.1829
C.V.	80.259	34.667	29.788	43.576
Minimum	0.5000	21.000	4.0000	0.5000
Median	21.000	32.000	10.000	1.1250
Maximum	60.000	60.000	15.000	1.9200

The heading of "Age" here represents the pooled data across all of the studies. In addition pooled and individual study histograms are presented below as a visual representation of this data. The marker for Study 106 is different as that data is expressed here in MONTHS, rather than years. In the table above, for easier comparison across the studies, the ages have been converted to fractional years.



This data clearly shows a problem with the proposed indication calling for usage down to 6mos of age. The only data available in lice infested children comes from study 103, in that study there are only 3 subjects below the age of 8 and no subjects below the age of 4. In Study 106 where infants were studied from 6-2yrs of age, only 3 subjects were below

the age of 1 yrs and there were only 8 subjects who completed all phases of the trial (it was originally designed, per protocol, to include "approximately 14 subjects"). Thus we have no data in lice infested children below the age of 4, and only limited data below the age of 8. The absorption data in the youngest studied age group, although using a higher concentration (1.8%), is also limited by the extremely small number of subjects at this vulnerable age group. While not convinced there is excessive absorption that will occur, it is this reviewer's opinion that the sponsor has not proven this either.

A consult was requested from the Office of Clinical Pharmacology Pediatric Staff through Dr. Gilbert Burckart of the OCP/Immediate Office, their consult is attached. Their conclusions, as presented in their review are:

> *-Extending the indication of Spinosad for the treatment of head lice i* (b) (4)
>
> *-Adding a Post Marketing Requirement (PMR) for the following:*
> - *Exposure (PK) data in patients < 2years of age with Pediculosis*
> - *Immature non-clinical toxicology study looking at repeated exposure to assess safety in patients < 2 years of age*
> - *Additional safety studies in patients 6 months to 2 years with repeated exposure*
>
> *-Benzyl alcohol is an ingredient of this formulation. The Division should consider including neonatal gasping syndrome under Warnings and Precautions although this product is not indicated for use in neonates.*

Since this consult was requsted it has been learned that the application will receive a C/R due to manufacturing "problems". Based on this the Medical Officer has concluded in their review that additional clinical data is necessary for approval of this product (b) (4) To that extent the Agency is going to recommend a new clinical trial (in which additional pk data can be obtained) in the younger age group. The pharmtox comment will be forwarded to the pharmtox reviewer for consideration.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

These elements were not addressed, nor would they be expected to impact the bioavailability of a pediculocide product for topical application.

2.4.2 Drug-drug interactions

Drug-drug interactions were not and are normally not evaluated for topically applied products.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not Applicable

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

As previously mentioned, the products in the NDA program were manufactured to contain 0.5%, 1.0% and 2.0% as total spinosyns. The lots would have a label claim of (b) (4) as spinosyn (A+D) respectively. Ultimately the sponsor elected to pursue the 0.9% product for marketing. This is of some relevance as the 1.8% product was used in the clinical pharmacology studies. As it represents a higher concentration than what is proposed for marketing (and no blood levels were detected, in vivo) this is acceptable.

The (b) (4) formulation (b) (4) used in pivotal Phase 3 trials. In the study report they are referred to as 1.0% formulations of spinosad. This value was revised to 0.9% after consultation with the FDA as to the way in which related species were referred to.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

A waiver of in vivo BE data is not necessary, as the (b) (4) formulation (b) (4) used in pivotal Phase 3 trials.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not Applicable

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

All of the pk studies (Study 101-04/ Study 106-06/ Study 103-05) used a LC/MS/MS system (b) (4)

2.6.2 Which metabolites have been selected for analysis and why?

The selection of spinosad A and D was done based on early decisions as to the predominate species present in the spinosad fraction. Other forms of spinosad do exist and are treated as "related" species. No metabolites were identified and a metabolic scheme in man does not exist.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

N/A

2.6.4 What bioanalytical methods are used to assess concentrations?

In general terms Spinosad A and Spinosad D are extracted (b) (4)

(b) (4)

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The linear range of the method was 3 to 1000 ng/mL for both spinosad A and D. Given the results, the working range was more than adequate.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

For both spinosyn A and D, the LOQ was the LOD (as reported), the %CV for both forms at 3ng/ml was less than 7% and at the low standard (9ng/mL) it was 5%. Based on this we have high confidence that the results are accurate, it also suggests that the assay could have been pushed lower, as the low %CV at the 3ng/mL level indicates to this reviewer that the assay had potentially "more to give".

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

For all three studies, the daily standard curve was constructed using 3, 5, 10, 25, 100, 250, 500, 825 and 1000ng/ml and with-in run QC standards at 9, 500, and 800ng/mL for both A and D forms.

For Studies Study 101-04/ Study 106-06 the analytical procedure appears to have been performed in an adequate manner with acceptable accuracy, precision, and selectivity. Problems were, however, encountered with Study 103-05 as for both spinosyn A and D, there were problems in the QC valiadation resulting in failing the for spinosyn A assay for 2 of the 3 runs.

Analytical Run Number	Date Extracted	Spinosyn A Status	Spinosyn D Status
001	19-Aug-2005	Rejected	Accepted
002	29-Aug-2005	Rejected	Not Applicable
003	01-Sep-2005	Accepted	Not Applicable

Note: Run001 was rejected for Spinosyn A due to the low QC samples failing to meet the bias acceptance criteria. Run002 failed to meet the acceptance criteria for calibration standards for Spinosyn A, where divergent calibration lines were observed.

While a standard curve was constructed at the beginning and the end of the study, there is too little data to evaluate to truly characterize this assay one way or the other. On the one hand, it is good that they were paying attention to the assay and did not blindly report the data without interpretation; on the other hand it does suggest that either lax procedures or lack of skill was present in the performance of the assay itself or the preparation of the calibration standard for run 002.

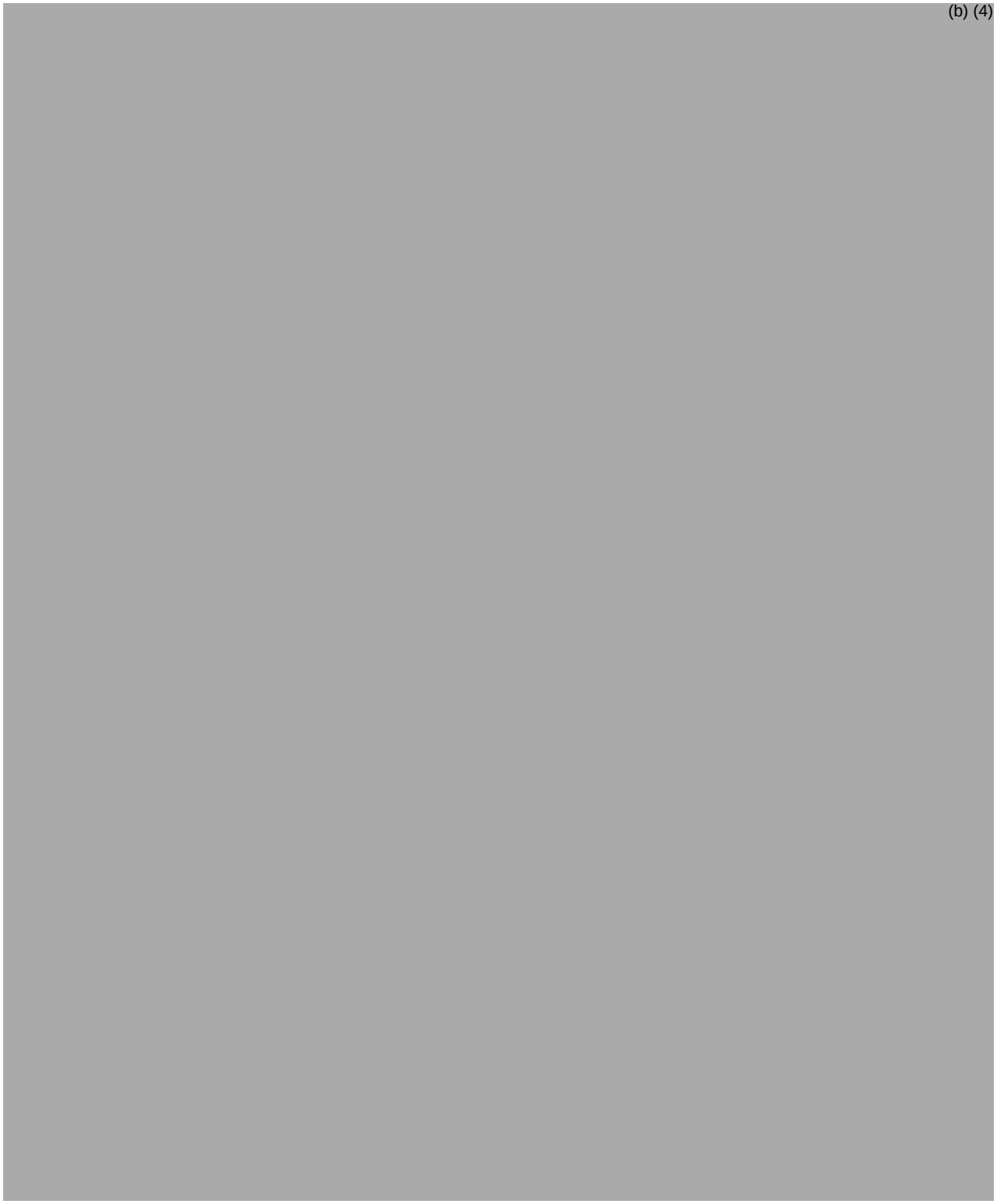
2.7 Labeling

The sponsor has proposed the following labeling specific to clinical pharmacology-pharmacokinetics. The text has been revised to both highlight the one study that was done in subjects with lice infestation and to indicate the proper analytical technique used. There is some concern mentioning the 1.8% product strength as that will not be available in the market, but it does, through the lack of systemic exposure, highlight the low systemic availability of the product. Green text indicates additions.

While the NDA does contain the results of an in vitro absorption study, as in vitro tests do not replicate the clinical situation (normal skin, non-viable, non-infested) inclusion of these results is not warranted here.

ANALYTICAL METHODS OVERVEIW

(b) (4)



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Title of Study:
A Single Treatment, Pharmacokinetic and Tolerance Study of NatrOVA Topical Cream (1%) in Pediatric Subjects 6 to 24 Months of Age

Investigator(s): W. Michael Brown, M.D.

Study Center(s): Hill Top Research
6699 13th Avenue North
St. Petersburg, FL 33710

Publication (reference): N/A

Studied period:

Screening Dates:	December 13, 2006
Date of first enrollment:	December 17, 2006
Date of last completed:	December 17, 2006

Objective(s): The objective of the study was to determine the topical absorption and safety of (b) (4) 1% Spinosad product for a single, 10 minute treatment in children 6 to 24 months of age.

Methodology:
All qualified subjects were treated with a topical application of 1% NatrOVA cream rinse which was applied on the scalp and left in place for 10 (ten) minutes. On Day 1, plasma samples for determination of drug concentrations were collected at 0 (pre-treatment), 1 and 4 hours post-treatment. Following the sample collections on Day 1, subjects were released from the clinic. Safety was assessed throughout the study by monitoring of skin evaluations, adverse events, and by laboratory assessments. Laboratory assessments (full CBC and serum chemistry) were conducted at the screening visit and at the conclusion of Day 1 (4 hours post-treatment).

Number of subjects (planned and analyzed):
Approximately 14 subjects, 6 to 24 months of age, were to participate in a screening visit to ensure that at least six (6) subjects complete all phases of the study. At least one subject was represented in each of the following age categories: 6 months, 7-10 months, 11-15 months, 16-20 months, 21-24 months. A total of eight subjects (4 male, 4 female) completed all phases of the study. One (1) subject completing the study was 6 months of age, two (2) subjects were 7-10 months of age, two (2) subjects were 11-15 months of age, one (1) subject was 16-20 months of age, and two (2) subjects were 21-24 months of age.

Diagnosis and main criteria for inclusion:
Children 6 to 24 months of age in good general health and that did not meet any of the exclusion criteria were eligible for enrollment in this study.

Test article, dose and mode of administration, batch number:
NatrOVA Topical Cream (1%), 30 mL of cream, topical application for 10 minutes, Lot Number: 7107.002A, Manufacture Date: 09/06/2006, Expiration Date: 09/2008

Duration of treatment:
A single 10 minute application was made on Day 1.

Reference therapy (dose and mode of administration, batch number):
None

Summary of Conclusions:

Efficacy Results:
There were no efficacy parameters measured in this study.

Safety Results:
Spinosad applied topically on the scalp (300 mg dose in approximately 30 mL of cream) for 10 minutes was safe based on safety determinations evaluated in this study. There were no observations of erythema or edema on any of the subjects' scalps at any of the assessment times during the study. There was no change in vital signs, laboratory tests or physical findings. A physician investigator reviewed the clinical laboratory data and recorded its significance and in all cases the findings were clinically not significant. These data are presented in section 14.3.4.

There were two adverse events, unrelated to the test article, reported by two subjects during the course of the study. Subject No. 103 experienced mild nasal congestion beginning on 12/14/06. The subject was given 1 tsp Equate Children's Cold & Cough on 12/16/06 and the symptom resolved on 12/17/06. Subject No. 108 experienced a mild low grade fever beginning on 12/16/06. The subject was given 0.6 mL of Infant Tylenol on 12/16/06 and the symptom resolved the following day. There were no serious adverse events.

Conclusions:
This was a single center, open-label study in pediatric subjects. Eight subjects were enrolled and eight subjects completed the study. All subjects were treated with a topical application of 1% Spinosad cream. Test compound (approximately 30 mL of cream) was applied on the scalp and left in place for 10 minutes. Plasma samples for pharmacokinetic analysis were collected at various time points after the topical administration and were analyzed by a validated method for Spinosyn A and Spinosyn D. The results of these determinations showed that the Spinosad as well as metabolite concentrations were below the limit of quantification in all samples collected. Thus there was no measurable systemic exposure after topical administration of Spinosad cream. The product was safe as determined by adverse events, skin evaluations, laboratory tests and physical findings.

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Title of Study:

A SINGLE TREATMENT, PHARMACOKINETIC AND TOLERANCE STUDY OF SPINOSAD TOPICAL CRÈME (2%) IN HEALTHY ADULTS.

Investigator(s):	Dyal Garg, Ph.D.
Study Center(s):	Hill Top Research, Inc. 900 Osceola Drive West Palm Beach, FL 33409
Publication (reference):	Not Applicable
Studied period:	This study was conducted over 7 days
Screening Dates:	December 4, 6, 7, 8, 2004
Date of first enrollment:	December 9, 2004
Date last subject completed:	December 21, 2004

Objective: The purpose of this study was to determine the plasma pharmacokinetic profile, topical and systemic tolerability following a single treatment with Spinosad 2% crème formulation in healthy adults.

Methodology: This was a phase I, single center, open-label study in healthy adult subjects. Twenty-three subjects were enrolled and 22 subjects completed the study. All subjects were treated with a topical application of 2% Spinosad crème. Test compound (30 gm of crème) was applied on the scalp and left in place for 10 (ten) minutes. Plasma samples for pharmacokinetic analysis were collected at 0 (pre-treatment), 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96 hours post application and on Day 7. Safety was assessed throughout the study by monitoring of adverse events, and by laboratory and vital signs assessments.

Number of patients (planned and analyzed):

Up to twenty-four subjects could have been enrolled in this study. Twenty three subjects were enrolled and twenty two completed the study.

Diagnosis and main criteria for inclusion:

Criteria for inclusion: Each subject must have had an appropriately signed Informed Consent agreement; Subjects had to be healthy males or females, 18 years or older who were within ± 30% of their ideal weight for height and frame size; Individuals in good general health, free of any systemic or dermatologic disorders which, in the opinion of the Principal Investigator/ medical consultant, or study monitor, would interfere with the study results or increase the risk of adverse events; Normal blood pressure (BP, systolic blood pressure ≤ 140 mmHg and diastolic blood pressure of ≤ 90 mm Hg) and a normal 12 lead ECG at screening; Females must have been postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or practicing one of the following methods of birth control: Condoms, sponge, foams, jellies, diaphragm, or intrauterine device; Hormonal contraceptives (oral, parenteral, or transdermal) for three months prior to screening; A vasectomized partner; Total abstinence from sexual intercourse (If hormonal contraceptives were used, the specific contraceptive must have been used for at least 3 months prior to screening. If the subject was currently using a hormonal contraceptive they also agreed to use a barrier method during this study and for 1 month after study completion); Normal values (at screening) for serum chemistry, hematology and urinalysis for subjects, unless both the principal investigator or qualified medical designee and the sponsor agreed that the abnormal value was not clinically significant; Subjects had to be euthyroid based upon Thyroid Function Tests (Total T3, Total T4, and TSH) within normal limits at screening or the abnormality could not be clinically significant.

Criteria for Exclusion: Individuals with any visible skin/scalp condition at the treatment site, in the opinion of the investigative personnel, or sponsor, that would interfere with the evaluation or absorption of drug; Individuals receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, or study monitor would interfere with the study results; Individuals with a history of drug abuse within the last year; Individuals previously treated with a pediculicide within 4 weeks of the study; Females who were pregnant or nursing. (Note: females of child-bearing potential must have had a negative urine pregnancy test prior to treatment [Day 1]); Sexually active females not using effective contraception; Individuals who, in the opinion of the investigator, did not understand the requirements for study participation and/or may have been likely to exhibit poor compliance.

Test article, dose and mode of administration, batch number:

All study materials were supplied by the study sponsor. Product was applied directly to the scalp (dry hair) by site personnel wearing latex free disposable gloves. The product was applied quickly and evenly, applying first to completely saturate the scalp and then to wet the hair from scalp outward. It was not necessary to saturate the hair completely. However, it was important to ensure that the scalp was completely wetted with the product. If subject had very long hair, there was a strong likelihood that the ends of the hairs would not be treated, but that was expected. Gloves and treatment bottle (2-oz High Density Polyethylene (HDPE) were weighed before and after treatment (using a digital scale that was calibrated).

Test product remained on the subject's scalp for 10 minutes (±30 seconds). The 10 minutes (±30 seconds) application time was measured from the end of the application of the product to the scalp and hair. The actual duration of application (from the start of application to the end of application) was collected and transcribed onto the subject's CRF. During this time, the subject was adequately supervised to minimize any risk from the subject touching or disturbing the treated hair/scalp.

After 10 minutes the hair and scalp were rinsed with warm water (for a minimum of 3 minutes). Subjects shielded their face and eyes using a suitably sized clean towel. Site personnel rinsed the subject's hair in such a manner to safeguard against water/product from directly running over the subject's face/eyes or into the ears. Following rinsing, the subject's hair was washed with a commercially available shampoo.

Summary of Conclusions:

Efficacy Results:

There were no efficacy parameters measured in this study.

Safety Results:

Spinosad applied topically on the scalp (600 mg dose in approximately 30 gm of crème) for 10 minutes was safe based on safety determinations evaluated in this study. There was no edema or erythema noted during the study. There was no change in vital signs, laboratory tests or physical findings. A physician investigator reviewed the clinical laboratory data and recorded its significance and in most cases the findings were clinically not significant. These data are presented in Table 14.2.6.

There were two adverse events in this study. One subject had cold symptoms during the study and one subject had a slight abnormality of TSH during the study. After thorough investigation of this abnormal finding, the investigators concluded that the fluctuations in this subject's TSH may be due to pre-existing sub-clinical hypothyroidism. As part of the study protocol, pharmacokinetic samples were collected for determination of plasma concentrations of Spinosad. The results of these determinations showed that the Spinosad as well as metabolite concentrations were below the limit of quantification in all samples collected in this patient. Elevated TSH in this subject was recorded as an adverse event, however, in the opinion of the investigators, the fluctuations in the TSH levels were not related to the study drug.

Both of the adverse events in this study were determined to be not related to product application and there were no serious adverse events.

Conclusions:

This was a single center, open-label study in healthy adult subjects. Twenty-three subjects were enrolled and 22 subjects completed the study. One subject was dropped due to poor veins and inability to draw blood samples for pharmacokinetic analysis. All subjects were treated with a topical application of 2% Spinosad crème. Test compound (approximately 30 gm of crème) was applied on the scalp and left in place for 10 (ten) minutes. Plasma samples for pharmacokinetic analysis were collected at various time points after the topical administration and were analyzed by a validated method for Spinosyn A and Spinosyn D.

The results of these determinations showed that the Spinosad as well as metabolite concentrations were below the limit of quantification in all samples collected. Thus there was no systemic exposure after topical administration of Spinosad crème. The product was safe as determined by adverse events, skin evaluations, vital signs, laboratory tests and physical findings.

STUDY 103

Title of Study: A SINGLE TREATMENT, PHARMACOKINETIC AND TOLERANCE STUDY OF SPINOSAD TOPICAL CRÉME (2%) IN PEDIATRIC SUBJECTS WITH PEDICULOSIS CAPITIS	
Investigator(s):	Dyal Garg, Ph.D.
Study Center(s):	Hill Top Research, Inc. 900 Osceola Drive West Palm Beach, FL 33409
Publication (reference):	Not Applicable
Studied period:	7-day period.
Screening Dates:	July 13, 20, 23, 30, 2005 & August 1, 3, 4, 2005
Date of first enrollment:	July 16, 2005
Date last subject completed:	August 13, 2005

Objective: The objective of this study was to determine the plasma pharmacokinetic profile and topical tolerability following a single treatment with the proposed Spinosad 2% créme formulation in pediatric subjects with *Pediculosis capitis*

Methodology: This was a phase I-B, single center, open-label, and single dose study in pediatric subjects. Fourteen subjects were enrolled and all subjects completed the study. All subjects were treated with a topical application of 2% Spinosad Créme. Test compound (30 mL of créme) was applied on the scalp and left in place for ten (10) minutes. Blood samples for pharmacokinetic analysis were collected at 0 (pre-treatment), 1, 2, 4, and 8 hours post application. Safety was assessed throughout the study by monitoring of adverse events, and by clinical laboratory tests, skin tolerability and physical examination.

Number of subjects (planned and analyzed):

Approximately twelve (12) pediatric subjects (ages $\geq$ 2 years and $\leq$ 18 years) with pediculosis capitis could be enrolled in this study with efforts to enroll at least four (4) subjects under the age of eight (8) years. Fourteen (14) subjects were enrolled and 14 subjects completed the study. The subject panel included three (3) subjects under the age of eight (8).

Diagnosis and main criteria for inclusion:

To participate in the test period of the study, subjects had to be male or female in good general health; from 2 to 18 years inclusive; and free of any systemic or dermatologic disorders which, in the opinion of the Principal Investigator or designee, would have interfered with the study results or increased the risk of adverse events; Subjects had to have head lice infestation with at least 3 live lice (adults and/or nymphs) and viable nits present at baseline, as determined by an examiner, as well as scalp irritation caused by lice infestation; Each subject must have an appropriately signed Informed Consent agreement; A parent (or guardian) must also sign an Informed Consent agreement and each subject must provide written consent and/or documented assent to participate in the study.

Subjects had to be available to stay in the clinic for blood draws. Parents or guardians also had to be available to stay in the clinic, with the minor subject, for the duration of the study. Subjects had to have veins capable of withstanding multiple blood draws as determined by the Principal Investigator or qualified phlebotomist; Normal values (at screening) for serum chemistry, hematology and urinalysis were required for subjects, unless both the principal investigator or qualified medical designee and the sponsor agreed that the abnormal value was not clinically significant.

Subjects must have been euthyroid based upon Thyroid Function Tests (Total T3, Total T4 and TSH) within normal limits at screening or the abnormality should not be clinically significant.

Test article, dose and mode of administration, batch number:

All study materials were supplied by the study sponsor. Product was applied directly to the scalp (dry hair) by site personnel wearing latex free disposable gloves. The product was applied quickly and evenly, applying first to completely saturate the scalp and then to wet the hair from scalp outward. It was not necessary to saturate the hair completely. However, it was important to ensure that the scalp was completely wetted with the product. If the subject had very long hair, there was a strong likelihood that the ends of the hairs would not be treated, but that was expected. Gloves and treatment bottle (2-oz High Density Polyethylene (HDPE) were weighed before and after treatment (using a digital scale that was calibrated).

Test product remained on the subject's scalp for 10 minutes (±30 seconds). The 10 minutes (±30 seconds) application time was measured from the end of the application of the product to the scalp and hair. The actual duration of application (from the start of application to the end of application) was collected and transcribed onto the subject's CRF. During this time, the subject was adequately supervised to minimize any risk from the subject touching or disturbing the treated hair/scalp.

After 10 minutes the hair and scalp were rinsed with warm water (for a minimum of 3 minutes). Subjects shielded their face and eyes using a suitably sized clean towel. Site personnel rinsed the subject's hair in such a manner as to safeguard against water/product from directly running over the subject's face/eyes or into the ears. Following rinsing, the subject's hair was washed with a commercially available shampoo. When all product had been removed, hair was shampooed and the rinsing water ran clean, subject's hair was gently towel dried. The hair was combed for 10 minutes with a lice comb to remove any residual product from the subject's head as well as lice and nits.

Summary of Conclusions:

Efficacy Results:

There were no efficacy parameters measured in this study.

Safety Results:

Spinosad applied topically on the scalp (600 mg dose in approximately 30 mL of créme) for 10 minutes was safe based on safety determinations evaluated in this study. Some subjects had slight to well defined erythema and/or edema prior to treatment. These conditions were most likely due to the presence of lice infestation in these subjects. There was no increase in edema or erythema noted during the study (see Table 14.2.1). There was no change in vital signs, laboratory tests or physical findings. A physician investigator reviewed the clinical laboratory data and recorded its significance and in most cases the findings were clinically not significant. These data are presented in Table 14.2.6.

There was one adverse event, fever for Subject # 112, reported during the study. This event occurred after the screening visit but resolved before the baseline/product treatment. Therefore, in the opinion of the Investigator, the event was not related to product application. There were no serious adverse events.

Conclusions:

This was a single center, open-label study in pediatric subjects infested with head lice. Fourteen subjects were enrolled and 14 subjects completed the study. All subjects were treated with a topical application of 2% Spinosad créme. Test compound (approximately 30 mL of créme) was applied on the scalp and left in place for 10 minutes. Plasma samples for pharmacokinetic analysis were collected at various time points after the topical administration and were analyzed by a validated method for Spinosyn A and Spinosyn D. The results of these determinations showed that the Spinosad as well as metabolite concentrations were below the limit of quantification in all samples collected. Thus there was no measurable systemic exposure after topical administration of Spinosad créme. The product was safe as determined by adverse events, skin evaluations, laboratory tests and physical findings.

4 Pages of Draft Labeling have been Withheld as B4 (CCI/TS) Immediately Following this Page

Office of Clinical Pharmacology

September 29th, 2009

Requester:	Dennis Batshaw, Pharm.D Office of Clinical Pharmacology, Division III
Drug:	Spinosad 0.9% (NDA-22408)
Brand name:	
Indication (approved):	Pediatric: • Treatment of head lice Adult: ▪ Treatment of head lice
Consult date:	September 21st, 2009
Reviewer:	Lily Mulugeta, PharmD
Consult Request:	Please comment on the (b) (4) cutoff for the indication of Spinosad in the treatment of head lice. (b) (4)

Infection with head lice is a widespread condition in developed and developing countries. Infection occurs most commonly in children, but also affects adults. If left untreated the condition can become intensely irritating and skin infections may occur if the bites are scratched. Currently, there are five FDA approved products for the treatment of head lice:

1. Permethrin cream rinse 1% (Nix and Rid): Information on dosing in children 2 years and older
2. Synergized pyrethrins (0.33% pyrethin, 4% piperonyl butoxide) shampoo and cream rinse: Approved in ages 2 years and older
3. Malathion 0.5% (Ovide): approved in patients 6 years and older
4. Lindane
5. Benzyl alcohol lotion 5% (Ulesfia): approved in patients 6 months and older

There is an emergence of drug resistance to existing therapy especially to Permethrin and pyrethrins which can result in treatment failure. Safety of these products is also a major consideration especially with the flammability of Malathion and the dermal absorption and resulting neurotoxicity of Lindane in younger pediatric patients.

Spinosad 0.9%) is a new product being developed for the control of human head lice (b) (4) Spinosad causes neuronal excitation in lice resulting in the paralysis and death. Spinosad is designed to be applied for a period of 10min. A sufficient amount should be applied to coat the entire hair shaft. After the application time, the hair is rinsed and

shampoo or other hair care products may be used. Re-application can be done in case of treatment failure.

The sponsor has submitted the following studies to support the indication in adults and children:

1. Six Phase 1 studies (3 PK/tolerability, one irritation/skin sensitization, one phototoxicity, and one photo-allergy)
2. Three Phase 2 studies (two dose ranging and one pilot)
3. Two Phase 3 studies (acute use, safety and efficacy in the treatment of *P. Capitis*)

The sponsor has conducted three PK/tolerability studies (SPN 101-04, SPN 103-05, and SPN106-06). Systemic concentration of Spinosad and Spinosad metabolite in the PK studies showed minimal dermal absorption with all concentrations being BLQ.

Table 2.7.2.2-1: Summary of Pharmacokinetic Evaluations in the Phase 1 Studies

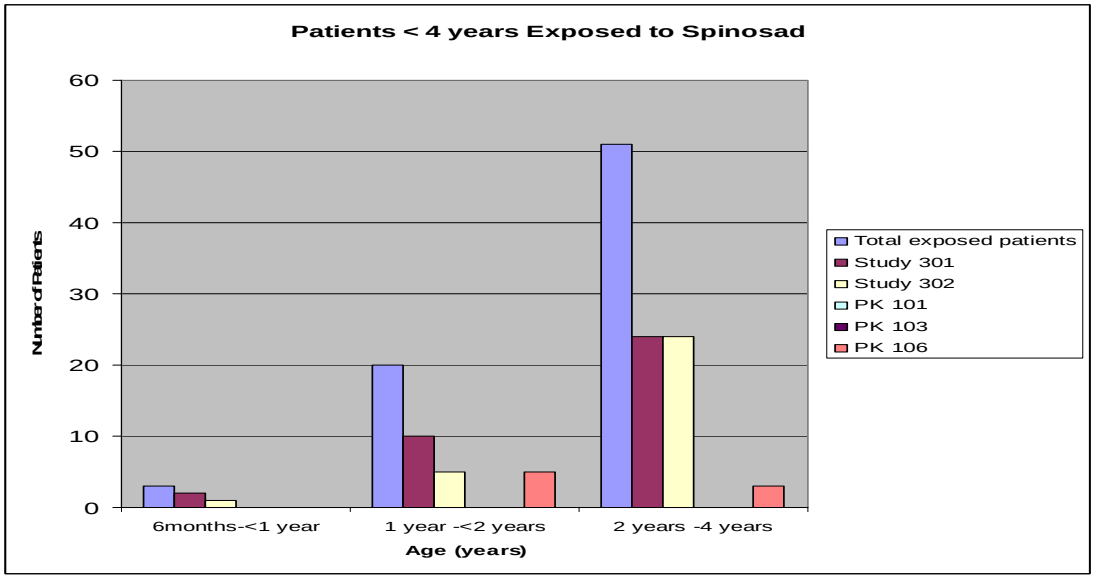
Study	Number of Samples (%)	Spinosad/Spinosad Metabolite Concentration
SPN-101-04	614 (100.0%)	BLQ[a]
SPN-103-05	136 (100.0%)	BLQ[a]
SPN-106-06	48 (100.0%)	BLQ[a]

[a] Below Limits of Quantification, i.e., <3 ng/mL

However, PK data is limited in patients younger than 4 years of age:

- Study 101 enrolled healthy adults 21-60 years of age.
- Study 103 was a single dose PK study in 14 subjects 4-15 years of age with P. Capitis. Of the 14 subjects, none were below the age of 4 years.
- Study 106 enrolled 8 ***healthy*** pediatric subjects 6-23 months of age only 5 of which were below the age of 2yrs and none below the age of 1 year.

Spinosad was well tolerated in the PK and efficacy/safety studies. A total of 74 patients below the age of 4 years were exposed to Spinosad: 3 patients aged 6 months to less than 1 year, 20 patients aged 1 year to less than 2 years and 51 patients aged 2 years to less than 4 years. The most commonly reported treatment-related adverse events in the studies were eye irritation (reported only in the NIX treatment group), ocular hyperaemia, application site erythema, and application site irritation. Clinically significant changes in lab value were not reported. There was no significant difference in treatment related local reaction, laboratory, or physical findings in patients younger than 4 years compared to older pediatric patients. However, the numbers are too small in the age group below 2 years to draw conclusion on the safety of Spinosad in that age group. Juvenile animal toxicology studies were not submitted by the sponsor in support of this indication.



EPA toxicity profile for Spinosad:

According to the EPA, the existing Spinosad data indicates that Spinosad possesses low acute toxicity via the oral, dermal, and inhalation routes of exposure. EPA does not consider Spinosad a dermal irritant, dermal sensitizer or eye irritant. No dermal toxicity was seen at the limit dose in a 21-day dermal toxicity study in rabbits. No developmental effects were seen in the rat and rabbit developmental toxicity studies. No developmental effects were seen in the rat and rabbit developmental toxicity studies. (http://www.epa.gov/EPA-PEST/2009/September/Day-23/p22534.htm)

Reviewer's Comment:
Spinosad is a neurotoxin. However dermal absorption seems minimal based on submitted in-vitro studies, short treatment duration, and systemic exposure data in patients older than 4 years of age. The sponsor has submitted data to support safety and efficacy in patients 6 months and older. However, the number of patients below the age of 2 years, with or without head lice, exposed to Spinosad is not sufficient to establish the safety of Spinosad in this age group.

A total of 51 patients between 2 to 4 years were exposed to Spinosad (95% with active disease). Systemic exposure data is not available in this age group. However, based on the lack of significant treatment related adverse events with Spinosad and a small potential for significant difference in dermal absorption rate compared to older patients, the available safety and efficacy data may support Spinosad's indication for treatment of Pediculosis C. (b) (4).

<u>The Division should consider</u>:
-Extending the indication of Spinosad for the treatment of head lice to patients (b) (4)

-Adding a Post Marketing Requirement (PMR) for the following:

- *Exposure (PK) data in patients < 2years of age with Pediculosis*
- *Immature non-clinical toxicology study looking at repeated exposure to assess safety in patients < 2 years of age*
- *Additional safety studies in patients 6 months to 2 years with repeated exposure*

-Benzyl alcohol is an ingredient of this formulation. The Division should consider including neonatal gasping syndrome under Warnings and Precautions although this product is not indicated for use in neonates.

References:

1. Sponsor's submission NDA 22408.
2. Pharmacology review: NDA 22408 (Spinosad)
3. Jones K, English J. Review of Common Therapeutics Options in the United States for the Treatment of Pediculosis Capitis. Clinical Infectious Diseases 2003; 36: 1355-61.
4. Lebwohl M, Clark L, Levitt J. Therapy for head lice based on life cycle, resistance and safety considerations. *Pediatrics.* 2007; 119(5):965–974
5. Stough D, Shellabarger S, Quiring J, et al. Efficacy and Safety of Spinosad and Permethrin Crème Rinses for Pediculosis Capitis. Pediatrics 124 (3): 2009, pp 389-395
6. Centers for Disease Control and Prevention. CDC factsheet. Available at: www.cdc.gov/lice/head/factsheet.html. Accessed August 22, 2008
7. http://www.epa.gov/EPA-PEST/2009/September/Day-23/p22534.htm

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/

EDWARD D BASHAW
10/06/2009