NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	022408/S-010
Priority or Standard	Standard
Submit Date(s)	28 February 2020
Received Date(s)	28 February 2020
PDUFA Goal Date	28 December 2020
Division/Office	Divison of Dermatology and Dentistry/Office of Inflammation and Immunology
Review Completion Date	18 December 2020
Established/Proper Name	spinosad
(Proposed) Trade Name	NATROBA
Pharmacologic Class	505(b)(1)
Code name	N/A
Applicant	ParaPRO, LLC
Dosage form	topical suspension, 0.9%
Applicant proposed Dosing Regimen	Apply product to skin by rubbing it in to completely cover the body from neck down to the soles of the feet. (b) (4) patients should also apply product to the hairline, temples, and forehead. Allow product to soak into the skin and dry for 10 minutes before getting dressed. Showering or bathing should occur no earlier than 6 hours after treatment.
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of scabies infestations in adult and pediatric patients four (4) years of age and older.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	81000006 |Pediculosis capitis (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the topical reatment of scabies infestations in adult and pediatric patients four (4) years of age and older.
Recommended Dosing Regimen	Apply NATROBA to skin by rubbing it in to completely cover the body from neck down to the soles of the feet. Patients with balding scalp should also apply NATROBA to the scalp, hairline, temples, and forehead. Allow NATROBA to absorb into the skin and dry for 10 minutes before getting dressed. Leave on the skin for at least 6 hours before showering or bathing.

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DDD = Division of Dermatology and Dentistry
DMEPA = Division of Medication Error Prevention and Analysis
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
ORDPURM = Office of Rare Diseases, Pediatrics, Urology & Reproductive Medicine
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Statistical Team Leader	Mohmed Alosh, PhD	OB/DB III	Sections: 7.2, 8.1, 8.3	Select one: ___ Authored ✓ Approved
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Glossary

AE	adverse event
AUC_{0-12h}	area under the concentration-time curve from time 0 to 12 hours
BA	benzyl alcohol
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma drug concentration
CMH	Cochran-Mantel-Haenszel
CRO	clinical research organization
DCN	Division of Cardiology and Nephrology
DDD	Division of Dermatology and Dentistry
DPMH	Division of Pediatric and Maternal Health
ECG	electrocardiogram
FDA	U.S. Food and Drug Administration
HPLC	high-performance liquid chromatography
ICH	International Conference on Harmonisation
IND	investigational new drug
iPSP	Initial Pediatric Study Plan
IRB	Institutional Review Board
IP	investigative product
ITT	intent-to-treat
I-ITT	index intent-to-treat
LOCF	last observation carried forward
LLOQ	lower limit of quantification
LSR	local skin reaction
NDA	new drug application
PK	pharmacokinetics
PMR	postmarketing requirement
POC	proof-of-concept
SAE	serious adverse event
SD	standard deviation
SAP	statistical analysis plan
sNDA	supplemental new drug application
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed plasma drug concentration

1. Executive Summary

1.1. Product Introduction

The Applicant, ParaPro, LLC, submitted an efficacy supplement to new drug application (NDA) 022408, NATROBA (spinosad) topical suspension, 0.9%, under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the treatment of scabies in patients 4 years of age and older. Spinosad, the active ingredient, is a natural substance derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. It is a mixture of two chemicals, spinosyn A and spinosyn D. Spinosad causes prolonged overexcitation of the insect nervous system, followed by paralysis and death.

NATROBA is currently approved for the topical treatment of head lice infestations in adult and pediatric patients 6 months of age and older.

The proposed dosing is as follows: Apply NATROBA to skin by rubbing it in to completely cover the body from neck down to the soles of the feet. Patients with balding scalp should also apply NATROBA to the scalp, hairline, temples, and forehead. Allow NATROBA to absorb into the skin and dry for 10 minutes before getting dressed. Leave on the skin for at least 6 hours before showering or bathing.

1.2. Conclusions on the Substantial Evidence of Effectiveness

To establish the efficacy of NATROBA in the treatment of scabies in patients 4 years of age and older, the Applicant submitted two multicenter, randomized, double-blind, vehicle-controlled Phase 3 studies: SPN-303-15 (minus the pharmacokinetics (PK) subjects) and SPN-304-15. These studies evaluated a single application of NATROBA topical suspension, 0.9% to the skin of the neck down to the soles of the feet and left on skin for a minimum of 6 hours before bathing/showering. Follow-up evaluations were conducted after 28 days. A total of 551 subjects 4 years of age and older (index subjects with scabies and household members) were enrolled across two studies, 296 NATROBA subjects and 255 vehicle subjects. The primary efficacy endpoint was the percentage of index subjects with complete cure of scabies at Day 28. Complete cure was defined as both clinical and dermatoscopic/microscopic cure, including the absence of all clinical signs and symptoms of scabies, with a negative microscopy and dermatoscopy.

In SPN-303-15 (Study 303), the index intent-to-treat (I-ITT) population was composed of 86 subjects. Study 303 was underpowered because the data from one center was removed from the analysis. In addition, the conclusions regarding Study 303 depend on how subjects with missing data were handled in the analysis. One subject was lost to follow-up and an additional four subjects had clinical assessments at Day 28 but did not have microscopic assessments. In the studies submitted by the applicant, among subjects with both clinical assessments and microscopic assessments, all subjects who met the criteria for a clinical cure also met the criteria for a complete cure (i.e., meeting the criteria for clinical cure was fully predictive of

meeting the criteria for complete cure). Thus, it is reasonable to assume that subjects who met the criteria for a clinical cure, but did not have a microscopic assessment can be assumed to have met the criteria for a complete cure. The Applicant presented an observed-case analysis in the study report that removed all five subjects with partial or completely missing data from the analysis. The Applicant's analysis of the primary endpoint of complete cure at Day 28 was not statistically significant (p=0.059). However, if subjects with completely missing data have their complete cure status imputed per the criteria specified in the protocol, and subjects missing microscopic assessments have their complete cure status imputed using their clinical cure status, there was a statistically significant difference between the NATROBA group compared to the vehicle group (69.8% versus 46.5%, p=0.0175).

In SPN-304-15 (Study 304), the I-ITT population was 120 subjects. Five subjects discontinued the study prior to Day 28. The Applicant presented an observed-case analysis in the study report that removed all five subjects with missing data from the analysis. The analysis of the primary endpoint of complete cure at Day 28 that followed the protocol-specified methods for handling subjects with missing data was statistically significant (83.9% NATROBA, 34.5% vehicle, p<0.001). The Applicant's observed-case analysis presented in the study report was also statistically significant (p<0.001).

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

The Applicant submitted an efficacy supplement to new drug application (NDA) 022408 for NATROBA (spinosad) topical suspension, 0.9% for the treatment of scabies in patients 4 years of age and older. Spinosad is a natural substance derived from the fermentation of a soil actinomycete bacterium, *Saccharopolyspora spinosa*. It is a mixture of two chemicals, spinosyn A and spinosyn D. Spinosad causes prolonged overexcitation of the insect nervous system, followed by paralysis and death.

To establish the effectiveness of spinosad in the treatment of scabies in patients 4 years of age and older, the Applicant presented results from two Phase 3 studies, SPN 303-15 (Study 303) and SPN 304-15 (Study 304), that evaluated a single topical application of NATROBA topical suspension, 0.9% to the skin of the entire body from the neck to the soles of the feet and left on the skin for a minimum of 6 hours before showering or bathing. The studies enrolled a total of 551 subjects 4 years of age and older with scabies as well as household members of the index subject. The primary efficacy endpoint was the percentage of index subjects with complete cure of scabies at Day 28. Complete cure was defined as both clinical and dermatoscopic/microscopic cure, including the absence of all clinical signs and symptoms of scabies, with a negative microscopy and dermatoscopy. In Study 303, the index intent-to-treat (I-ITT) population included 86 subjects. At Day 28, 69.8% of the NATROBA group had achieved a complete cure compared to 46.5% of the vehicle group ($p=0.0175$). In Study 304, the I-ITT population was 120 subjects. At Day 28, 83.9% of the NATROBA group compared to 34.5% of the vehicle group had a complete cure ($p<0.001$).

To establish the safety of spinosad in the treatment of scabies in patients 4 years of age and older and household members of the index subjects, the Applicant presented the results of three studies: A proof-of-concept (POC) study, SPN-401-12, and the two Phase 3 trials, Study 303 and Study 304. The safety evaluations were adequate in type and frequency to identify local and systemic treatment-emergent adverse events (TEAEs). The safety population consisted of a total of 592 subjects who received at least one application of the study drug and were evaluated within 24 hours of removal. Treatment with NATROBA topical suspension, 0.9% was not associated with mortality or serious adverse events (SAEs). The most common adverse reactions were local skin reactions (LSRs), primarily application site irritation (including burning and application site pain, 2.5%) and dry skin (1.9%). All of the LSRs were mild in severity.

At this time, inspection of clinical sites is delayed due to travel restrictions and prioritization of mission-critical site inspections due to the COVID-19 pandemic.

In summary, scabies is a common parasitic infection that can affect patients of all ages. Because the mite is easily spread, all close contacts of

diagnosed scabies patients must all be treated at the same time. NATROBA (spinosad) topical suspension, 0.9% provides an additional treatment option for scabies. The available evidence of efficacy and safety supports a favorable overall benefit/risk assessment. Pending successful preapproval inspections of three clinical sites, the review team supports approval of NATROBA for the treatment of scabies in patients 4 years of age and older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Scabies is a parasitic condition caused by infestation with the mite *Sarcoptes scabiei var. hominis* that is readily transmitted by close contact. It often presents as serpiginous burrows accompanied by intense pruritus, in web spaces of the hands and genital area. Household members are easily susceptible, and if present in the genital area, can be transmitted by sexual contact. Scabies can affect all age groups but occur most commonly in children, sexually active adults, and populations in close proximity such as in dormitories, military barracks, and prisons. Scabies is diagnosed by clinical signs and symptoms such as burrows, nodules, and nocturnal pruritus. The diagnosis is confirmed by microscopy (skin scraping under oil) or dermatoscopy. Lesions may occur anywhere on the body but are most commonly seen on palms, soles, and warm, moist areas of the body such in skin folds and genitals. Because it is easily transmitted with close contact, scabies requires treatment of the patient and household members/sexual partners, even if asymptomatic. Residual pruritus may persist as long as 2 weeks after all the mites and eggs are killed due to hypersensitivity to the mite byproducts.	While scabies is not a life-threatening condition, it can have a significant adverse impact on the quality of life of a patient, as well as the family members and sexual partners. To ensure complete cure close contacts of affected patients should also be treated. .

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	The currently approved treatments for scabies include permethrin cream, 5%; crotamiton lotion, 10%; and lindane lotion/shampoo, 1%. There are several unapproved drugs that are widely used to treat scabies including topical sulfur, 5-10% in petrolatum ointment and oral ivermectin.	Permethrin cream, 5% is the most widely used drug currently approved for the treatment of scabies infestation and the only one safe for use in pediatric patients. Therefore, there is a need for other safe and efficacious treatment options for the treatment of scabies infestation in adult and pediatric populations.
Benefit	To establish the effectiveness of NATROBA (spinosad) topical suspension, 0.9% in the treatment of scabies in patients 4 years of age and older, the Applicant submitted results from two randomized, multicenter, vehicle-controlled, Phase 3 studies that evaluated topical application of NATROBA (spinosad) topical suspension, 0.9% applied to skin from the neck down to the soles of the feet and left on for a minimum of 6 hours before showering or bathing. The studies enrolled 551 subjects 4 years of age and older with scabies, as well as the household members of the patients. The primary endpoint was the percentages of subjects with complete cure at Day 28. In Study 303, the I-ITT population was 86 subjects. At Day 28, 69.8% of NATROBA group achieved a complete cure compared to 46.5% of the vehicle group (p=0.0175). In Study 304, the I-ITT population was 120 subjects. At Day 28, 83.9% of the NATROBA-treated subjects compared to 34.5% of the vehicle group had a complete cure, which was statistically significant (p<0.001).	Based on the available data, NATROBA (spinosad) topical suspension, 0.9% provides an effective treatment option for scabies in patients 4 years of age and older.
Risk and Risk Management	The Applicant comprehensively assessed the safety of NATROBA (spinosad) topical suspension, 0.9% in the treatment of scabies in patients 4 years of age and older. The POC and Phase 3 studies (SPN-401-12, Study 303, and Study 304) provided the primary safety database (N=592). These studies adequately reflected the expected	The size of the safety database and the scope of the safety analyses were sufficient to characterize the safety profile of NATROBA. The safety profile of NATROBA in the treatment of scabies infestation was similar to that in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	use in patients 4 years of age and older with scabies. There were no deaths or serious adverse reactions associated with NATROBA in these trials. Review of the safety data from three trials (SPN-401-12, Study 303, and Study 304) identified adverse reactions of application site irritation (including burning and application site pain) in 2.5% of subjects and dryness in 1.9% of subjects. The product labeling is sufficient to manage the identified risks for the proposed indication if approved.	treatment of lice infestation. Given the lack of any new safety signals, at-home use by the patient or caregivers is appropriate.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient-reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Scabies is a common skin condition that can affect people of all ages, races, and socioeconomic backgrounds. The offending agent is a microscopic, eight-legged mite, *Sarcoptes scabiei* var. *hominis.*

In 2013, scabies was named a neglected tropical disease by the World Health Organization. In resource-poor countries and in tropical areas, scabies can be endemic where overall community prevalence can be up to 20 to 30%, and up to 50% of the pediatric population. In the U.S., outbreaks are common. Populations at greatest risk are those in close proximity, including schoolchildren, crowded households, prisons, dormitories, nursing homes, and those displaced by natural disasters. Children, elderly, and immunocompromised populations may experience more severe disease. Separately, scabies is also considered a sexually-transmitted disease when transmitted during sexual contact and localized to the genital/pubic area. Any person affected by scabies may be an asymptomatic carrier.

Clinically, the mite creates serpiginous burrows as it travels through the skin and lays eggs, particularly in intertriginous areas such as the genitalia, axillae, web spaces of the hands and feet, and waistband. Once established, the mite completes its entire 30-day lifecycle burrowed in the epidermis of its host. Females lay 3 eggs per day, which take 10 days to mature before the young mite can reproduce. The mite can transfer from one host to another with skin-to-skin contact. It can live as long as 3 days without a host, so transmission indirectly through fomites is another route of infestation. Sensitization to the proteins in the mite feces results in highly pruritic papules which can become vesicular. With an initial infestation, it may take 2 to 6 weeks before the host experiences clinical symptoms due to lack of sensitization. However, once sensitized, lesions can manifest within 24 to 48 hours with subsequent infestations. Itch is a pronounced symptom, usually worse at night. If treatment is delayed, then excoriated lesions may be exacerbated by superinfection with *Streptococcus pyogenes* (Group A strep), *Staphylococcus aureus*, and postinfection complications.

Diagnosis can be made clinically or by microscopy/dermatoscopy. To diagnosis by microscopy, a mineral oil preparation is typically done. A superficial scraping of the skin in an area with a black dot is most likely to yield evidence of the mite, such as an egg, scybala (feces), or the mite itself. Alternatively, it may be possible to examine a black dot under dermatoscopy which may reveal a mite. In the event that microscopy and/or dermatoscopy are negative (because most patients only have fewer than 100 mites on them), treatment is still recommended if clinical symptoms are consistent with scabies.

To clear an infestation, treatment must be directed toward killing the mites and/or the eggs. Due to the superficial location of the mite on the skin, most treatments are topical and require full body application from below the neck to the feet, paying particular attention to the creases and folds of the body as well as web spaces between fingers and toes. Infants are more likely to

get lesions on the palms, soles, face, scalp, and neck. To avoid spread and reinfection, close contacts of patients with scabies, including asymptomatic household members and sexual partners, must also be treated at the same time. Because mites can live 2 to 3 days away from the human host, bedding, clothes, and towels must be washed with hot water and dried at high heat. Pets are not affected by the *Sarcoptes scabiei* var. *hominis* mite and do not need to be treated.

Commonly, postscabitic itch lingers for a couple weeks after the mites are killed due to continued hypersensitivity to by-products and until the affected stratum corneum is shed. Symptoms are typically managed with antipruritics, topical corticosteroids, and antihistamines.

2.2. Analysis of Current Treatment Options

All treatments for scabies are topical prescription products; there are no over-the-counter therapies. While the initial treatment may kill the active mites, some eggs may survive. A repeat treatment may be necessary to cover newly-hatched mites.

The current first-line therapy for scabies is permethrin cream, 5%. It is also considered the most effective and safest of the currently approved treatments for scabies, and thus the most widely prescribed. It was first approved by the U.S. Food and Drug Administration (FDA) in 1986. The mechanism of action is to inhibit sodium transport in neurons of arthropods, thereby causing paralysis. It kills both mites and eggs. The most common adverse reaction is brief stinging on the skin after application. The treatment may be repeated (b) (4) if necessary.

The following products are also FDA-approved for the treatment of scabies: crotamiton lotion, 10% and lindane lotion/shampoo, 1%.

Crotamiton lotion, 10% was approved by the FDA in 1955 for the treatment of scabies in adult patients. It is also approved for the symptomatic treatment of pruritic skin. Common adverse reactions are skin irritation and allergic sensitivity.

Lindane lotion or shampoo, 1%, an organochlorine agent used in pesticides, was first approved by the FDA in 1951 for treatment of head lice and scabies. Due to reports of neurotoxicity (such as seizures) and death through the MedWatch Program, the FDA issued a Public Health Advisory in 2003 (U.S. Food and Drug Administration 2015) to warn patients of these potential serious adverse events (SAEs). These cases occurred primarily as a result of overuse or unintended ingestion. Similar effects could potentially occur with a single application in patients at risk for increased systemic absorption, including those who weigh less than 110 pounds, children, elderly, and patients with a compromised skin barrier. Thus, the FDA added a Box Warning to the lindane label, revising the scabies indication as a second-line therapy for adults with scabies who have failed or have an intolerance to other treatments, and contraindicated in premature infants and individuals with known uncontrolled seizure disorders; warning of the risk of neurologic toxicity; and emphasizing the proper use of lindane (Olta Pharmaceuticals et al. 2003).

There are several unapproved products cited by the Centers for Disease Control for the treatment of scabies infestations (Centers for Disease Control and Prevention 2019).

- Sulfur, 5 to 10%, compounded in a petrolatum base was frequently prescribed as an alternative to lindane or crotamiton prior to the approval of permethrin. The most common regimen is three applications of the product at 24-hour intervals. Sulfur is reported to be irritating, malodorous, and easily staining.

Oral ivermectin, an antiparasitic drug, has been used off-label for the treatment of scabies at doses of 200 to 400µg/kg on day 1 with a second dose 2 weeks later (Chandler and Fuller 2019).

Table 1. Treatment Armamentarium Relevant to Scabies

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues Other Comments
FDA approved treatments				
Permethrin cream, 5%	Scabies in patients 2 months of age and older	1986	Apply to skin from neck down to soles of feet, rinse off in 8-14 hours	Pediatrics: Approved for infants ≥2 months Pregnancy Category B Breastfeeding: Safety not established Allergic contact dermatitis in individuals with sensitivity to formaldehyde
Crotamiton lotion, 10%	Scabies in adult patients	1955	Apply to skin from chin down to feet, repeat full-body application in 24 hours; rinse off in 48 hours after 2nd application	Pediatrics and breastfeeding: Safety not established Pregnancy Category C, though no animal studies Irritant contact dermatitis, especially in denuded skin
Lindane lotion or shampoo, 1%	Scabies in adults who have failed or cannot tolerate other treatments	1951 (Revised 1995)	Apply 1 ounce to skin from neck down for 8-12 hours	Pediatrics: Box warning due to potential neurotoxicity in patients <110 lbs/50 kg (infants and children), elderly, and conditions with compromised skin barrier Pregnancy Category C, though not recommended Breastfeeding: Safety not established
Other unapproved treatments commonly used				
Precipitated sulfur, 5-10%, in petrolatum	Scabies in all patients, including under 2 months	N/A	Topically overnight for 3 successive days	Irritating
Ivermectin (3 mg tablets)	Not FDA-approved for scabies but commonly prescribed off-label	N/A	Oral dose of 200-400 µg/kg on day 1 and repeat on day 8 or 14	Pediatrics: Safety not established for children weighing <33 lbs/15 kg; potential CNS toxicity in infants and young children Pregnancy Category C, though not recommended Breastfeeding mothers: Safety not established

Source: Reviewer
Abbreviations: CNS, central nervous system; N/A, not applicable

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

NATROBA (spinosad) topical suspension, 0.9% was approved by the FDA on January 8, 2011, for the treatment of head lice in patients 4 years of age and older. Efficacy supplement 5 was approved on December 30, 2014, expanding the age range down to patients 6 months of age and older.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed NATROBA (spinosad) topical suspension, 0.9% under investigational new drug (IND) 066657.

On July 19, 2019, the FDA provided comments in advance of a scheduled July 22, 2019, pre-supplemental NDA (sNDA) meeting. In the premeeting comments, the FDA discussed these points in response to the Applicant's questions:

- The FDA recommended the inclusion of details of the PK evaluation for benzyl alcohol, as measurable levels were detected following a single topical application of NATROBA, to include the bioanalytical method validation reports and bioanalysis reports of all the analyses.
- The FDA emphasized the necessity of presenting safety assessments based on pooled data to enhance the ability to support efficacy conclusions and to detect an association between drug use and an adverse event (AE). Pooled data should also be used to assess the effect of demographic and other characteristics of subjects to support meaningful conclusions.
- The FDA requested an explanation for the high vehicle response rate (55.4% in Study 303 and 37% in Study 304) in the two Phase 3 trials.

The Applicant accepted these comments and subsequently cancelled the July 22, 2019, meeting.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Rationale for Site Selection

Three clinical investigator (CI) sites were chosen based on numbers of enrolled subjects, magnitude of efficacy results, protocol deviations, as well as prior inspection history.

1. Jeffrey C. Seiler, MD (Site 101 in Study 303)
   LSRN Research
   6758 N. Military Trail
   Suite 110
   Palm Beach, FL 33407

2. Thomas S. Turk, MD (Site 206 in Study 304)
   Discovery Clinical Trials
   110 E. Savannah
   Suite A-201 and A-204
   McAllen, TX 78503

3. Christopher M. Chappel, MD (Site 106 in Study 303 and Site 211 in Study 304)
   The Chappel Group Research
   2711 N. Orange Blossom Trail
   Kissimmee, FL 34744

At the time of this review, the inspection of selected clinical sites is pending due to travel restrictions and prioritization of mission-critical site inspections due to the COVID-19 pandemic.

4.2. Product Quality

Not applicable for this supplemental application

4.3. Clinical Microbiology

Not applicable for this supplemental application

4.4. Devices and Companion Diagnostic Issues

Not applicable for this supplemental application

5. Nonclinical Pharmacology/Toxicology

A Pharmacology/Toxicology review is not needed for this efficacy sNDA submission.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant is developing NATROBA (spinosad) topical suspension, 0.9% for the treatment of scabies infestations in patients 4 years of age and older. Spinosad belongs to the class of insecticides derived from the fermentation process of naturally occurring soil actinobacterium, *Saccharopolyspora spinosa.*

NDA 022408 for NATROBA (spinosad) topical suspension, 0.9% was first approved on January 18, 2011, for the topical treatment of head lice infestation in patients 4 years of age and older. On December 30, 2014, NATROBA (spinosad) topical suspension, 0.9% was approved for usage in patients with head lice infestation 6 months of age and older. The dosing regimen for NATROBA (spinosad) topical suspension, 0.9% is to apply a sufficient amount of product to cover dry scalp, then apply to dry hair, leave on for 10 minutes, then thoroughly rinse off with warm water, and repeat treatment only if live lice are seen 7 days after first treatment.

In the current submission, using the same formulation currently approved for the treatment of head lice, the Applicant intends to establish the safety and effectiveness of NATROBA in the treatment of scabies infestations in patients 4 years and older. The proposed dosing regimen for NATROBA (spinosad) topical suspension, 0.9% is a single treatment, applying the product to the skin and rubbing it in to completely cover the body from the neck down to the soles of the feet ((b) (4) patients should also apply product to the hairline, temples, and forehead), allowing product to soak into the skin, and showering or bathing no earlier than 6 hours after treatment.

To support the indication for treatment of scabies infestations, this NDA consists of three studies: A Phase 2 (Note: The Applicant defined this study as Phase 4) proof-of-concept (POC) study (SPN-401-12) and 2 similarly-designed pivotal Phase 3 safety and efficacy studies (Study 303 and Study 304). The Phase 3 studies were identical in design, with the exception that only Study 303 was conducted in 2 parts: a PK study and a primary study. In addition, Study 303 included PK evaluations in the PK study and clinical laboratory evaluations for all Study 303 subjects.

6.1.1. Recommendations

From a clinical pharmacology standpoint, the totality of data provided in this sNDA support the approval of NATROBA at the proposed dosing regimen for the treatment of scabies infestations in patients 4 years of age and older.

6.1.2. Postmarketing Requirement and Commitments

Conduct a pharmacokinetic (PK) and safety study to assess the effect of NATROBA in pediatric subjects 1 month to 3 years 11 months of age with scabies infestation. The study should aim for

a total enrollment of 50 subjects and a minimum of 16 completers in the PK evaluation, with an adequate number of subjects in the lowest age range.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant evaluated the PK of NATROBA (spinosad) 0.9% and the ingredient benzyl alcohol in a total of 19 pediatric subjects, 5 to 16 years of age, who received open-label NATROBA, as a part of the Phase 3 study (Study 303).

No subject in the PK population had measurable concentrations of spinosyn A or spinosyn D at any time up to 12 hours postapplication. As such, no concentration data or PK parameters were available for these metabolites.

A few subjects in the PK population had measurable concentrations of benzyl alcohol at the 0.5 (n=5), 1.0 (n=2), and 3.0 (n=2) hour postapplication time points; however, no subject had measurable concentrations of benzyl alcohol at either the 6.0- or 12.0-hour postapplication time points. The arithmetic mean concentrations of benzyl alcohol were 2.51, 2.14, and 2.35 µg/mL at the 0.5-, 1.0-, and 3.0-hour assessment time points, respectively. Based on the available plasma concentration data, the mean maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}), and area under the concentration-time curve from time 0 to 12 hours (AUC_{0-12h}) values for benzyl alcohol were 2.74 µg/mL, 1.42 hours, and 19.24 µg•h/mL, respectively. As a side note, only one subject (ID: 101-PK-15) had quantifiable AUC_{0-12h} (19.24 µg•h/mL), which was estimated from concentrations at three time points, namely, 0.5-, 1.0- and 3.0-hour postapplication.

The PK data indicated no systemic exposure for either spinosyn A or spinosyn D, and the systemic exposure for benzyl alcohol up to 12.0-hour postapplication was low among pediatric subjects who used a single topical, whole-body application of NATROBA. There were no unexpected safety signals or adverse safety trends observed during the study. Overall, NATROBA was generally safe and well-tolerated in subjects 4 years of age and older after a single, whole-body application of study drug. Although there were no 4-year-old subjects in the PK cohort, based on lack of systemic exposure of spinosyn A or spinosyn D, low systemic exposure of benzyl alcohol, and no systemic safety signals from the Phase 3 trials that included 4-year-old subjects, the available PK data in subjects 5 years of age and older would support approval in subjects down to 4 years of age.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The efficacy and PK results in Phase 3 trials (Study 303 and Study 304) appear to support the acceptability of the proposed dosing regimens for patients 4 years of age and older.

The product is designed to apply to the skin by rubbing it in to completely cover the body from the neck down to the soles of the feet. Patients with balding scalp should also apply NATROBA to the scalp, hairline, temples, and forehead. Allow the product to absorb into the skin and dry for 10 minutes before getting dressed. Leave on the skin for at least 6 hours before showering or bathing.

Therapeutic Individualization

Not applicable.

Outstanding Issues

There are no outstanding issues that would preclude the approval of NATROBA for the treatment of scabies infestations in subjects 4 years of age and older from a Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacokinetics

As a part of a multicenter, double-blind, Phase 3 study (Study 303), an open-label PK study was conducted in a subset of pediatric subjects with scabies infestation. The PK bioavailability study was completed in 19 subjects, 5 to 16 years of age, to determine the PK profile of NATROBA (spinosad) topical suspension, 0.9% and the ingredient benzyl alcohol. All subjects applied a single treatment of NATROBA (spinosad) topical suspension, 0.9% from the neck down to the soles of the feet and allowed treatment to remain on the body for a minimum of 6 hours, after which the study drug was washed off. Subjects underwent plasma sampling over a 12-hour period at predose, 0.5, 1.0, 3.0, 6.0, and 12 hours post-treatment. Plasma spinosad concentrations were below the limit of quantification (3 ng/mL) in all samples.

In this study, the systemic levels of benzyl alcohol were assessed to address the safety concerns of gasping syndrome. Systemic exposure to benzyl alcohol at a concentration of ~109.2 µg/mL (1.01 mmol/L) has been associated with neonatal gasping syndrome (Gershanik et al. 1982). In the PK study, benzyl alcohol was quantifiable (above 1 µg/mL) in a total of 9 plasma samples in 6 out of 19 subjects (32%): three out of ten subjects in the 5- to 9-year age group and three out of nine subjects in the 10- to 16-year age group. The highest observed concentration was 3.94 µg/mL at 0.5 hours post-treatment but below limit of quantification at 1 hour post-treatment for one subject in the 10- to 16-year age group. There were two subjects with a benzyl alcohol concentration at 3 hours post-treatment with the highest value of 3.53 µg/mL for one subject in the 5- to 9-year age group. Plasma concentrations were below limit of quantification (1 µg/mL) at the 3.0-hour time point for all other subjects; no subject had measurable concentrations at the 6.0-and 12.0-hour time points. The mean (SD) C_{max}, T_{max}, and AUC_{0-12h} values for benzyl alcohol were 2.74 (1.11) µg/mL, 1.42 (1.24) hours, and 19.24 (-)

µg•h/mL, respectively. The highest plasma benzyl alcohol observed in the current study was 2.74 µg/mL (about 40-fold lower than the level of concern).

In the current submission, using the same formulation currently approved for the treatment of head lice, the Applicant intended to establish the safety and effectiveness of NATROBA in the treatment of scabies infestations administered as a single treatment. According to the MUsT results (PK bioavailability study under maximal usage conditions) in 19 pediatric subjects 5 to 16 years of age, the systemic exposure for spinosyn A and spinosyn D was not quantifiable, and systemic exposure for benzyl alcohol up to 12-hours post-treatment was limited, which demonstrates similar bioavailability to that observed in the head lice studies in the original NDA submission.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Efficacy was not established in the clinical pharmacology study as the maximal use study was conducted to assess the systemic safety of this product. Efficacy of the product is supported by the results of the Phase 3 trials.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the patient population based on the safety and efficacy results of the Phase 3 trials.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No alternative dosing regimens or management strategy are required.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food does not impact the bioavailability of topically administered drugs. Since there were no quantifiable systemic levels of spinosyn A or spinosyn D and this is a single dose treatment, drug interaction does not appear to be of any concern.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

In support of their sNDA, the Applicant submitted the following studies:

- 3 Clinical Studies in Scabies Subjects
  - SPN-401-12 – A randomized, double-blind, vehicle-controlled proof-of-concept study; 1 U.S. study center
  - SPN-303-15 (Study 303) with two parts:
    - Primary study: A randomized, double-blind, vehicle-controlled Phase 3 study at 4 U.S. study centers
    - PK study: An open-label PK study at 3 U.S. study centers
  - SPN-304-15 (Study 304) – A randomized, double-blind, vehicle-controlled Phase 3 study, 7 U.S. study centers

The table below provides a summary of the aforementioned studies submitted for NATROBA (spinosad) topical suspension, 0.9% to treat scabies in patients 4 years of age and older.

Table 2. Listing of Clinical Studies Conducted with NATROBA Topical Suspension, 0.9% in the Treatment of Scabies

Study Identity	Study Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled studies to support efficacy and safety							
SPN-401-12 (POC)	Randomized, double-blind, 2-arm, 28-day, vehicle-controlled	Single topical application after confirmed diagnosis of scabies for 6 hours in subjects >18 years of age[1]	Primary – Percentage of index subjects with complete cure of scabies at Day 28	Single topical application with 28-day follow-up	21 (16 NATROBA, 5 vehicle)	7 M, 14 F; 18-63 years old	1 U.S. study center
Study 303 Primary Study (Phase 3)	Randomized, double-blind, 2-arm, 28-day, vehicle-controlled	Single topical application after confirmed diagnosis of scabies for 6 hours in subjects >4 years of age	Primary – Percentage of index subjects with complete cure of scabies at Day 28	Single topical application with 28-day follow-up	271 (142 NATROBA, 129 vehicle)	128 M, 143 F; 4-89 years old	4 U.S. study centers[2]
Study 304 (Phase 3)	Randomized, double-blind, 2-arm, 28-day, vehicle-controlled	Single topical application after confirmed diagnosis of scabies for 6 hours in subjects >4 years of age	Primary – Percentage of index subjects with complete cure of scabies at Day 28	Single topical application with 28-day follow-up	280 (154 NATROBA, 126 vehicle)	117 M, 145 F; 4-79 years old	7 U.S. study centers[3]
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
Study 303 PK Study (Phase 3)	Open-label study to evaluate pharmacokinetics	Single topical application after confirmed diagnosis of scabies for 6 hours in subjects 4-16 years of age	Secondary – Analysis of the PK variables	Single topical application with PK assessed over the first 12 hours	20 subjects (NATROBA only)	12 M, 8 F; 5-16 years	3 U.S. study centers[2]

Source: Adapted from Applicant, Mod 2.5 Clinical Overview
[1] Only 1 subject per household was enrolled; other household members were provided with permethrin, 5% in order to prevent household re-infestation.
[2] Of the 5 planned study centers in Study 303, study center 104 data was excluded from the primary study; only 3 of the 5 centers (not including study center 104) enrolled subjects in the PK study.
[3] Of the 11 planned study centers, 8 screened at least 1 subject; 7 screened and randomized at least 1 subject; 3 did not screen or randomize any subjects.
Abbreviations: F, female; M, male; PK, pharmacokinetic; POC, proof-of-concept

7.2. Review Strategy

The Applicant conducted three clinical studies (SPN-401-12, Study 303, and Study 304) in subjects with scabies.

SPN-401-12 was a Proof-of-Concept study evaluating 21 subjects with scabies. The Applicant later completed two similar Phase 3, randomized, double-blind, vehicle-controlled, multicentered studies (Study 303 and Study 304) to evaluate the efficacy and safety. In addition, Study 303 included an open-label, 12-hour study in 20 pediatric subjects to study the PK of NATROBA.

The studies were conducted in the United States from January-March 2013 (SPN-401-12) and June 2017 to July 2018 (Study 303 and Study 304). The primary endpoint was the proportion of subjects achieving clinical and microscopic cure of scabies at Day 28.

For the efficacy evaluation, only Study 303 (excluding the PK subjects) and Study 304 subjects were assessed. For the safety evaluation, all subjects in all three studies who had at least one application of the study drug were included.

Data Sources

The data sources used for the evaluation of the efficacy and safety of NATROBA for the treatment of scabies included the Applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format. The application did not include the electronic datasets in the initial submission. Following an information request to submit the datasets and supporting documentation, the Applicant submitted Study Data Tabulation Model and analysis datasets. The analysis datasets used in this review are archived at \\CDSESUB1\evsprod\nda022408\0071\m5\datasets\.

Data and Analysis Quality

The databases required minimal data management prior to performing analyses. The Applicant submitted statistical programs for generating study report tables.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Studies Used to Support Efficacy

8.1.1. Studies 303 and 304

Study Design

Study 303 and Study 304 were Phase 3, randomized, double-blind, vehicle-controlled trials that evaluated NATROBA versus vehicle in the treatment of scabies. The studies enrolled index subjects, defined as the youngest member in a household (≥4 years of age) with an active scabies infestation, and up to 5 additional members of each index subject's household (regardless of scabies infestation status). An active scabies infestation was defined as the presence of clinical signs and symptoms (evidence of burrows or scabies lesions and pruritus) as well as microscopic evidence from a skin scraping or dermatoscopy, to demonstrate the presence of mites, eggs, and/or scybala.

Index subjects were randomized in a 1:1 ratio to NATROBA or vehicle, stratified by study site. The planned sample size was 120 index subjects per study. All subjects in the same household received the same treatment (NATROBA or vehicle). All index subjects and household contacts were treated with a single application of NATROBA or vehicle on Day 1, applied to the entire body from the neck down to the toes (including the soles of the feet) and if balding, to the scalp, hairline, temples, and forehead. The topical suspension was left on the skin for 6 hours before bathing.

Subjects were evaluated for irritation and AEs on Day 2, received a telephone call on Day 14 to report AEs and receive instruction on preventing re-infestation, and were evaluated on Day 28 for efficacy and safety assessments. Subjects who were not cured at Day 28 were provided with permethrin, 5% as rescue medication.

Study 303 also included a separate open-label PK evaluation cohort. This cohort included additional pediatric subjects, 4 to 16 years of age, that did not reside in an index subject's household. The planned sample size for the PK cohort was 24 subjects. All subjects in the PK cohort were treated with NATROBA. The Applicant included the subjects in the PK cohort in the safety population of Study 303.

Study Endpoints

Scabies assessments included clinical signs and symptoms and microscopic examination or dermatoscopy as follows:

- Evidence of burrows (yes/no)
- Inflammatory/noninflammatory lesion counts
- Evidence of pruritus (yes/no)
- Microscopy/dermatoscopy result (positive/negative)

The primary efficacy endpoint was complete cure at Day 28, defined as clinical cure (all signs and symptoms completely resolved) and microscopic cure (absence of mites, eggs, and scybala), and negative dermatoscopy for burrows. The primary efficacy endpoint was evaluated in the index subjects.

The protocol did not specify any secondary endpoints but specified several exploratory endpoints. The exploratory endpoints were defined as:

- The percentage of subjects with clinical cure at Day 28
- The percentage of subjects with microscopic cure at Day 28
- The number of new lesions at Day 28
- The change from baseline in total lesion counts at Day 28
- The percentage of subjects in the ITT population (index plus household) who were infested at baseline and had complete cure at Day 28

Statistical Analysis Plan

The primary analysis population was the index intent-to-treat (I-ITT) population, defined as all index subjects who were randomized. Subjects will be analyzed as randomized. Additional analysis populations included:

- Safety population, defined as all subjects who received a single administration of study product (index subjects plus household members plus PK cohort). Subjects were analyzed as treated.
- ITT population, defined as all subjects who were randomized (index subjects plus household members). Subjects were analyzed as randomized.
- Index per protocol population, which excluded subjects who did not have scabies assessments performed, subjects who received the wrong treatment, discontinued prior to Day 28, missed the Day 2 appointment, used another scabicide, or used prescription or over-the-counter medicated lotions.
- PK protocol, defined as all pediatric PK subjects who gave consent, were eligible, and had blood drawn for PK assessment.

The primary efficacy endpoint of complete cure at Day 28 was analyzed with a Cochran-Mantel-Haenszel (CMH) test stratified by study site (with pooling of small sites with fewer than 8 index subjects per arm).

It should be noted that the statistical analysis plan (SAP) did not specify how confidence intervals (CIs) for the treatment effect estimates would be calculated. In the study reports, the Applicant presented CIs for the treatment difference based on the chi-square statistic that did not adjust for analysis center.

A sensitivity analysis was conducted using logistic regression with terms for study site and treatment group. The SAP allowed for additional baseline characteristics or covariates to be added “if appropriate.”

The SAP stated that subjects who discontinued before Day 28 due to a lack of efficacy or a drug-related AE would have their complete cure status imputed as nonresponders. Alternatively, subjects who discontinued due to lost-to-follow-up or other reasons were to have their complete cure status imputed using last observation carried forward (LOCF). Note, however, that because efficacy assessments were only conducted on Day 1 and Day 28, any subject in the I-ITT population would be imputed as nonresponders even if LOCF was used. As sensitivity analyses, missing data would be handled using observed cases, LOCF (as noted above, this would not differ from the primary imputation method), and with multiple imputation. The multiple imputation analysis used the fully conditional specification method separately for each treatment arm.

For the exploratory endpoints, the binary endpoints were analyzed with a CMH test stratified by study site. The number of new lesions was analyzed with a negative binomial regression model with terms for treatment and study site, and baseline lesion count as a covariate. The change from baseline in total lesion count was analyzed with analysis of covariance with terms for treatment and study site, and baseline lesion count as a covariate.

The protocol did not specify any methods for controlling multiplicity across the exploratory endpoints.

Protocol Amendments

No significant changes were made to the protocol after subjects began enrollment. The Applicant made some minor changes to the protocol regarding the handling of missing data and the criteria for pooling small sites after enrollment began.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that studies were designed, monitored, and conducted in accordance with good clinical practice requirements and ethical principles. Study protocols, the subject information and informed consent forms, and subject recruitment procedures were reviewed by the responsible Institutional Review Board (IRB). The Applicant obtained an approval from the IRB prior to study initiation.

Financial Disclosure

Refer to Appendix 14.2.

Patient Disposition

Study 303 enrolled 364 subjects (176 randomized to NATROBA, 160 randomized to vehicle, and 28 subjects in the PK cohort treated with NATROBA). Of these subjects, 64 were index subjects randomized to NATROBA and 65 were index subjects randomized to vehicle. Six subjects (three index subjects and three household subjects) received a different treatment than they were

randomized to. Following completion of the study, FDA informed the Applicant that one of the investigators in Study 303 (Site 104) was indicted for conspiracy to commit wire and mail fraud, fraudulently obtaining controlled substances, and furnishing false information to the U.S. Drug Enforcement Administration related to actions in a different clinical trial. Thus, the Applicant reanalyzed the data excluding the data from Site 104, which had enrolled 34 subjects (21 index subjects) on the NATROBA arm, 31 subjects (22 index subjects) on the vehicle arm, and 8 subjects in the PK cohort. The I-ITT population excluding Site 104 is the primary efficacy analysis population. In this population, one subject from each treatment arm discontinued the study.

All index subjects in the I-ITT population were treated with their randomized treatment. One household subject was randomized to NATROBA but was treated with vehicle. An additional five subjects enrolled at Site 104 (which was excluded from the efficacy and safety analyses) were randomized to vehicle but were treated with NATROBA (see Table 3).

Table 3. Disposition of Subjects in Study 303

Disposition	NATROBA	Vehicle	NATROBA PK Cohort
Including site 104			
Enrolled (as randomized)	176	160	28
Safety population (as treated)	180	156	28
Index subjects (as randomized)	64	65	
Excluding site 104			
ITT (as randomized)	142	129	20
Safety population (as treated)	141	130	20
Index subjects (I-ITT) (as randomized)	43	43	
Completed Day 28 visit	42 (98%)	42 (98%)	
Reasons for discontinuation			
Lost to follow-up	1 (2%)	--	
Other (subject not eligible for enrollment)	--	1 (2%)	

Source: pg. 58 of the study report for Study 303 and reviewer analysis.
Abbreviations: I-ITT, index intent-to-treat; ITT, intent-to-treat; PK, pharmacokinetics

Study 304 enrolled 280 subjects (154 randomized to NATROBA and 160 randomized to vehicle). One center (Site 202) did not comply with randomization procedures. While 18 subjects were enrolled at this center (9 subjects randomized to NATROBA and 9 subjects randomized to vehicle with only 1 subject enrolled per household in each case), all subjects were treated with vehicle. The issue was identified during the study and the Applicant terminated the site. The 18 subjects from Site 202 are excluded from efficacy analyses but are included in safety analyses (as treated). The I-ITT population excluding Site 202 is the primary efficacy analysis population. In this population, one subject on the NATROBA arm and four subjects on the vehicle arm discontinued the study (see Table 4).

Table 4. Disposition of Subjects in Study 304

Disposition	NATROBA	Vehicle
Enrolled (as randomized)	154	126
Safety population (as treated)	145	135
ITT (as randomized, excluding Site 202)	145	117
Index subjects (I-ITT) (as randomized, excluding Site 202)	62	58
Completed Day 28 visit	61 (98%)	54 (93%)
Reasons for discontinuation		
Lost to follow-up	--	2 (4%)
Withdrawal of consent	1 (2%)	2 (4%)

Source: pg. 49 of the study report for Study 304 and reviewer analysis.
Abbreviations: ITT, intent-to-treat; I-ITT, index intent-to-treat

Protocol Violations/Deviations

The most common protocol violation was "procedure not done." For the five NATROBA subjects in Study 303 with this protocol violation, four subjects did not have a skin scraping performed for microscopic assessment conducted at the Day 28 visit and one did not have labs done at screening. Because complete cure was defined as both clinical cure and microscopic cure at Day 28, the fact that some subjects did not have skin scrapings performed at Day 28 had an impact on the efficacy assessments (see Table 5).

Table 5. Protocol Violations (I-ITT)

	Study 303		Study 304	
Violation	NATROBA N=43 n (%)	Vehicle N=43 n (%)	NATROBA N=62 n (%)	Vehicle N=58 n (%)
Protocol deviations	7 (16)	4 (9)	2 (3)	2 (3)
Procedure not done (skin scrapings at Day 28 or labs at screening)	5 (12)	--	--	--
Consent/assent (delays in signing informed consent)	--	2 (5)	--	1 (2)
Timing of assessments (delays in labs at screening)	1 (2)	1 (2)	--	--
Visit window violation	2 (5)	--	2 (3)	1 (2)
Inclusion/exclusion violation	--	1 (2)	--	--
Product violation	1 (2)	--	--	--

Source: pg. 243 of the study report for Study 303 and pg. 178 of the study report for Study 304 and reviewer analysis.
Abbreviations: I-ITT, index intent-to-treat

Table of Demographic Characteristics

The baseline demographics among the index subjects were generally balanced across the treatment groups in the two studies. The mean age was approximately 39 years. A slightly higher proportion of subjects were female than male. A large majority of subjects were white in Study 303 (93%) and in Study 304 (67%) to a lesser extent. Seven percent of the subjects enrolled in Study 303 and 23% of subjects enrolled in Study 304 were black or African-American. Approximately 70% of subjects in Study 303 and 46% of subjects in Study 304 were Hispanic or Latino (see Table 6).

Table 6. Demographics in Studies 303 and 304 (I-ITT)

	Study 303		Study 304	
Demographic Parameter	**NATROBA N=43**	**Vehicle N=43**	**NATROBA N=62**	**Vehicle N=58**
Age (years)				
Mean	38.0	38.8	40.1	39.7
Range	6-74	7-80	4-76	5-71
4-17 years	6 (14)	12 (16)	11 (18)	7 (12)
18-64 years	33 (77)	27 (63)	43 (69)	48 (83)
65+ years	4 (9)	4 (9)	8 (13)	3 (5)
Gender,				
Female	25 (58)	23 (53)	34 (55)	36 (62)
Male	18 (42)	20 (47)	28 (45)	22 (38)
Race				
White	39 (91)	41 (95)	42 (68)	38 (66)
Black or African-American	4 (9)	2 (5)	15 (24)	12 (21)
Other	--	--	1 (2)	2 (3)
Asian	--	--	4 (6)	4 (7)
American Indian/AK Native	--	--	--	--
Native HI/Pacific Islander	--	--	--	2 (3)
Ethnicity				
Not Hispanic or Latino	13 (30)	13 (30)	35 (56)	30 (52)
Hispanic or Latino	30 (70)	30 (70)	27 (44)	28 (48)

Source: pg. 59 of Study Report 303 and pg. 50 of Study Report 304 and reviewer analysis.
Data is expressed as n (%) unless otherwise specified.
Percentages may not sum to 100% due to rounding
Abbreviations: I-ITT, index intent-to-treat; AK, Alaskan; HI, Hawaiian

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Scabies clinical assessments at baseline included evidence of burrows, lesion counts, and evidence of pruritus. Subjects also underwent a microscopic examination or dermatoscopy. All index subjects had a positive microscopic/dermatoscopic result at baseline, and all but one subject had evidence of pruritus. The two studies differed in the percentage of subjects with evidence of burrows at baseline, and the range of baseline lesions. In Study 303, about half of the subjects had evidence of burrows at baseline, while nearly all subjects did in Study 304. Although the median number of baseline lesions for the two studies were similar (approximately 12 to 14 lesions) the range and variability were much larger in Study 303 than 304, with Study 303 enrolling more subjects at the two extremes (very few lesions and very many lesions). However, within each study, the baseline disease characteristics were balanced across treatment groups (see Table 7).

Table 7. Baseline Disease Characteristics (I-ITT)

	Study 303		Study 304	
Disease Characteristic	**NATROBA N=43**	**Vehicle N=43**	**NATROBA N=62**	**Vehicle N=58**
Evidence of burrows	20 (47)	23 (53)	61 (98)	57 (98)
Evidence of pruritus	43 (100)	42 (98)	62 (100)	58 (100)
Number of lesions				
Mean (SD)	19.4 (20.5)	17.5 (18.8)	13.0 (5.5)	12.8 (4.6)
Min, Q1, median, Q3, max	1, 3, 14, 36, 100	1, 3, 12, 25, 100	4, 9, 12, 15, 29	4, 10, 12, 15, 24
Microscopy/dermatoscopy positive	43 (100)	43 (100)	62 (100)	58 (100)

Source: pg. 60 of Study Report 303 and pg. 51 of Study Report 304 and reviewer analysis.
Data is expressed as n (%) unless otherwise specified.
Abbreviations: I-ITT, index intent-to-treat; SD, standard deviation; Q1, first quartile; Q3, third quartile

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No formal measurements of treatment compliance were performed; however study drug bottle weights were documented prior to and after use (regardless of where the application was performed, in the clinic or at home), and subjects (or parents of subjects) were queried regarding adherence to the application instructions and the time of removal. As part of the exclusion criteria, use of an alternative scabicide within four weeks was not permitted. Rescue treatment was not permitted until after study completion (28 days) or study discontinuation (if earlier than 28 days).

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was complete cure at Day 28, defined as clinical cure (all signs and symptoms completely resolved) and microscopic cure (absence of mites, eggs, and scybala), and negative dermatoscopy for burrows. The primary efficacy endpoint results for Study 304 demonstrate a robust and statistically significant treatment effect that is not impacted by study conduct issues or the method of handling missing data. However, the results for Study 303 were impacted by the decision to remove the data from Site 104 (which reduced the sample size substantially) and also the way in which missing data was handled. Decisions on how to handle these issues impacted both the magnitude of the treatment effect and whether or not the result met statistical significance criteria. This section will provide the Applicant's analyses and a variety of sensitivity and supportive analyses.

The primary efficacy endpoint was evaluated in the index subjects (I-ITT population). The primary efficacy endpoint was analyzed with a CMH test stratified by analysis center, which resulted from the pooling of small sites with fewer than eight index subjects per arm.

The SAP did not specify a method for calculating corresponding CIs. In the study reports, the Applicant presented p-values based on the CMH test and CIs for the treatment difference based on chi-square statistics that were not adjusted for analysis center. Unless otherwise noted, the CIs for the treatment difference presented in this review are based on CMH estimates that adjust for analysis center, and thus are consistent with the corresponding p-values.

In Study 303, three analysis centers were used: Site 101 (45 subjects), Site 103 (25 subjects), and 'Pooling Site 01' that included Site 102 (one subject), Site 105 (13 subjects), and Site 106 (two subjects). In Study 304, three analysis centers were used: Site 208 (45 subjects), Site 210 (35 subjects), and 'Pooling Site 01' that included Site 204 (three subjects), Site 206 (one subject), Site 209 (31 subjects), and Site 211 (five subjects).

The analyses for Study 303 excluded subjects from Site 104. Site 104 enrolled 43 index subjects which was one-third of the enrolled population of index subjects. The removal of this site from the analyses had a significant impact on the ability of the study to detect a treatment effect due to the significantly reduced sample size. The study was powered for a sample size of 120 subjects. The analyses for Study 304 excluded subjects from Site 202 because the site did not follow randomization procedures and all subjects were treated with vehicle. However, Study 304 enrolled the target of 120 index subjects.

In Study 303, one vehicle subject was withdrawn from the study on Day 19 when it was discovered that the subject did not meet the eligibility criteria for the study. The subject had data collected on Day 19 for the end-of-study assessment and was not considered to have missing data. The subject was observed to be a nonresponder at the end-of-study assessment on Day 19. In the NATROBA arm, five subjects had partial or completely missing efficacy data for the Day 28 assessment. One subject was lost to follow-up and no Day 28 efficacy assessments were conducted. The remaining four subjects were clinically assessed at the Day 28 visit, but did not have skin scrapings taken for microscopic evaluation. All four subjects were assessed as having achieved clinical cure, but had missing values for microscopic cure.

In Study 304, five subjects (one NATROBA and four vehicle) withdrew from the study prior to the Day 28 assessment and had missing efficacy data for all components of the Day 28 assessment.

The SAP specified methods for handling missing data: subjects who discontinued due to lack of efficacy or a drug-related AE would have their complete cure status imputed as nonresponders, and subjects who discontinued due to lost-to-follow-up or other reasons were to have their complete cure status imputed using LOCF. Note that because efficacy assessments were only conducted at baseline and Day 28, if a subject had missing data at Day 28, the prespecified imputation procedure would impute nonresponse regardless of whether LOCF or nonresponder imputation was used because all subjects were nonresponders at baseline.

Although the efficacy endpoint tables in the clinical study reports for Studies 303 and 304 state that missing data was imputed using the primary imputation method, the tables in the clinical study report actually present observed case analyses with no imputation for missing data. Table 8 details the observed case analyses presented in the study reports for Studies 303 and 304 as well as the analyses consistent with the SAP specifications for missing data handling. For this imputation, subjects missing either the microscopic cure assessment or both the microscopic and clinical cure assessment at Day 28 were imputed as nonresponders. The primary efficacy endpoint analysis for Study 304 was statistically significant ($p<0.001$) for both the observed case analysis and the analysis using data imputation. The primary efficacy endpoint analysis for

Study 303 was not statistically significant for either the observed case analysis (p=0.059) or the analysis using data imputation (p=0.1946).

Table 8. Complete Cure at Day 28 (I-ITT; Applicant's Imputations)

	Study 303		Study 304	
Parameter	**NATROBA N=43**	**Vehicle N=43**	**NATROBA N=62**	**Vehicle N=58**
Observed cases (from study report), n/N (%)	26/38 (68.4)	20/43 (46.5)	52/61 (85.2)	20/54 (37.0)
Treatment difference[a], %	19.7		49.0	
95% CI	(-1.4, 40.8)		(34.8, 63.1)	
P-value	0.059[b]		<0.001	
Missing data imputed per the SAP (missing as nonresponse), n/N (%)	26/43 (60.5)	20/43 (46.5)	52/62 (83.9)	20/58 (34.5)
Treatment difference, %	13.1		49.7	
95% CI	(-7.1, 33.2)		(36.0, 63.5)	
P-value	0.1946		<0.001	

Source: pg. 293 of Study Report 303 and pg. 189 of Study Report 304 and reviewer analysis.
[a] The Applicant presented treatment difference estimates and CIs based on the chi-square method rather than the Mantel-Haenszel method adjusting for analysis center. The estimated treatment effect and CI presented in the study reports are: Study 303- 21.9% (0.9%, 42.9%); Study 304- 48.2% (32.6%, 63.9%).
[b] The main body of the study report presents the p-value as 0.057 while the appendix presents the p-value as 0.059. The reviewer confirmed that 0.059 is correct p-value for the observed case analysis.
Abbreviations: I-ITT, index intent-to-treat; CI, confidence interval; SAP, statistical analysis plan

However, as noted above, four NATROBA subjects in Study 303 had clinical cure assessments, but not microscopic assessments at Day 28. All four subjects were assessed as having clinical cure at the Day 28 visit. The investigator noted that three of the subjects declined to have the skin scrapings conducted. For the fourth subject, the investigator noted that the skin scraping was not done but did not provide a reason. To assess the likelihood that these subjects would have had microscopic cures had the procedure been performed, the data for the other subjects who achieved clinical cure at Day 28 was broken down by whether these subjects achieved microscopic cure (negative microscopy) or not (positive microscopy). As seen in Table 9, out of the 118 subjects who achieved clinical cure across both treatment arms and both studies, no subject who achieved clinical cure had positive microscopy. Thus, it seems reasonable to assume that the subjects with observed clinical cure but missing microscopy can be imputed as having negative microscopy, because the combination of clinical cure plus positive microscopy was not observed in any subject in either of the two studies.

Table 9. Microscopy Results Among Subjects with Observed Clinical Cure at Day 28 (Index Subjects)

	Study 303		Study 304	
Result	**NATROBA N=43**	**Vehicle N=43**	**NATROBA N=62**	**Vehicle N=58**
Clinical cure	26	20	52	20
Clinical cure+negative microscopy	26	20	52	20
Clinical cure+positive microscopy	0	0	0	0

Source: Reviewer analysis

Thus, rather than imputing subjects with observed clinical cure but missing microscopy result as missing or as nonresponders, as shown in Table 8, based on the Applicant's study reports or as a direct application of the SAP-specified missing data handling rules, it may be reasonable to

impute such subjects as having achieved complete cure at Day 28. This reviewer recommends using the analyses in Table 10 as the primary analyses, as they maximize the use of observed data for subjects who attended the Day 28 visit, and use the SAP-specified method for imputing data for subjects who did not attend the Day 28 visit.

Table 10. Complete Cure at Day 28 (I-ITT; Recommended Imputation)

	Study 303		Study 304	
Parameter	**NATROBA N=43**	**Vehicle N=43**	**NATROBA N=62**	**Vehicle N=58**
Complete cure (recommended imputation)[1], n (%)	30 (69.8)	20 (46.5)	52 (83.9)	20 (34.5)
Treatment difference, %	22.7		49.7	
95% CI	(1.8, 43.5)		(36.0, 63.5)	
P-value	0.0175		<0.001	

Source: Reviewer analysis
[1] Subjects with observed clinical cure but missing microscopic cure imputed as complete cure; subjects with completely missing data imputed as nonresponders
Abbreviations: I-ITT, index intent-to-treat; CI, confidence interval

Even though Site 104 was excluded from the primary analyses, it may also be useful to consider the analyses that include Site 104. The treatment difference for Study 303 with Site 104 included is similar to the treatment difference with Site 104 excluded; however, including results from Site 104 increases the complete cure rates for both the NATROBA and vehicle arms. If the data from Site 104 were considered reliable and the study analyzed as designed, Study 303 would have met the statistical significance criterion for the primary endpoint under either proposal for handling missing data (See Table 11).

Table 11. Complete Cure at Day 28 (I-ITT; Study 303, Including Site 104)

	Study 303	
Parameter	**NATROBA N=64**	**Vehicle N=65**
Complete cure (imputation per SAP)[1], n (%)	47 (73.4)	36 (55.4)
Treatment difference, %	17.8	
95% CI	(2.9, 32.7)	
P-value	0.0192	
Complete cure (recommended imputation)[2], n (%)	51 (79.7)	36 (55.4)
Treatment difference, %	24.2	
95% CI	(9.0, 39.4)	
P-value	0.0017	

Source: Reviewer analysis.
[1] Missing data imputed as nonresponse
[2] Subjects with observed clinical cure but missing microscopic cure imputed as complete cure; subjects with completely missing data imputed as nonresponders
Abbreviations: CI, confidence interval; I-ITT, index intent-to-treat; SAP, statistical analysis plan

To further consider the impact of missing data on the results, a "worst case" analysis that imputes NATROBA subjects as nonresponders and vehicle subjects as responders was conducted by this reviewer. A total of one subject (NATROBA) in Study 303 and five subjects (one NATROBA and four vehicle) in Study 304 did not have efficacy assessments at Day 28. For Study 303, if the subjects with observed clinical cure but missing microscopic assessment are considered to have achieved complete cure, there is only one subject with no assessments at Day 28. This subject was treated with NATROBA and was imputed as a nonresponder in the

analysis in Table 10. Thus, the results of the 'worst case' analysis are the same as the analysis presented in Table 10 for Study 303. For Study 304, the 'worst case' imputation imputes the four subjects with missing data in the vehicle arm as responders (see Table 12). The 'worst case' imputation in Study 304 reduces the treatment effect by approximately 7%, but the p-value remains <0.001.

Table 12. 'Worst Case' Imputation for the Primary Efficacy Endpoint (I-ITT; Worst Case Imputation)

	Study 303		Study 304	
Parameter	**NATROBA N=43**	**Vehicle N=43**	**NATROBA N=62**	**Vehicle N=58**
Complete cure (worst case imputation)[1], n (%)	30 (69.8)	20 (46.5)	52 (83.9)	24 (41.4)
Treatment difference, %	22.7		42.8	
95% CI	(1.8, 43.5)		(28.4, 57.2)	
P-value	0.0175		<0.001	

Source: Reviewer analysis
[1] NATROBA subjects imputed as nonresponders; vehicle subjects imputed as responders
Abbreviations: I-ITT, index intent-to-treat; CI, confidence interval

Components of the Primary Endpoint and Other Exploratory Endpoints

The protocols included five exploratory endpoints that included the two components of the primary endpoints (clinical cure at Day 28 and microscopic cure at Day 28), two endpoints based on lesion counts (the number of new lesions at Day 28 and the change from baseline in total lesion counts at Day 28), and one endpoint looking at the complete cure rate at Day 28 of index subjects plus household members infested at baseline. None of these analyses were adjusted for multiplicity. Descriptive statistics will be presented for these endpoints.

As discussed above, all subjects who had observed clinical cure also had microscopic cure; thus, the response rates for clinical cure are the same as complete cure, if the subjects with observed clinical cures, but missing microscopic cures are assumed to have microscopic cure (and thus complete cure). The microscopic cure rates are higher, as some subjects did not meet the criteria for clinical cure, but met the criteria for microscopic cure (see Table 13).

Table 13. Exploratory Endpoints – Components of Complete Cure (I-ITT; Recommended Imputation[a])

	Study 303		Study 304	
Parameter	**NATROBA N=43 n (%)**	**Vehicle N=43 n (%)**	**NATROBA N=62 n (%)**	**Vehicle N=58 n (%)**
Complete cure	30 (69.8)	20 (46.5)	52 (83.9)	20 (34.5)
Clinical cure	30 (69.8)	20 (46.5)	52 (83.9)	20 (34.5)
Microscopic cure	34 (79.1)	26 (60.4)	55 (88.7)	25 (43.1)

Source: reviewer analysis
[a] Subjects with observed clinical cure but missing microscopic cure at Day 28 are imputed as having microscopic cure and complete cure. Subjects without Day 28 clinical assessments are imputed as not meeting the clinical cure or microscopic cure definition.
Abbreviations: I-ITT, index intent-to-treat

The trend for the change from baseline in lesions was greater on the NATROBA arm than the vehicle arm in both studies (see Table 14).

Table 14. Exploratory Endpoints – Lesion Counts (I-ITT; LOCF)

	Study 303		Study 304	
Parameter	**NATROBA N=43**	**Vehicle N=43**	**NATROBA N=62**	**Vehicle N=58**
Baseline lesions				
Mean (SD)	17.5 (18.8)	19.4 (20.5)	13.0 (5.5)	12.8 (4.6)
Median	12	14	12	12
Day 28 lesions				
Mean (SD)	6.8 (21.0)	11.4 (16.1)	2.8 (11.2)	6.9 (6.6)
Median	0	0	0	7
Change from baseline				
Mean (SD)	-12.6 (14.8)	-6.1 (14.7)	-10.2 (10.3)	-5.9 (7.0)
Median	-8	-3	-10.5	-5
New lesions				
Mean (SD)	0.98 (4.3)	1.86 (3.1)	1.3 (8.9)	1.4 (2.3)
Median	0	0	0	0

Source: reviewer analysis
Abbreviations: I-ITT, index intent-to-treat; LOCF, last observation carried forward; SD, standard deviation

The final exploratory endpoint considered the complete cure rate at Day 28 among all subjects infested at baseline (index plus household). Study 303 included an additional 45 household members infested at baseline and Study 304 included an additional 41 household members infested at baseline. The complete cure rates among household subjects were consistent with the rates among index subjects, except the treatment effect among household subjects in Study 303 was slightly larger than among index subjects due to a lower vehicle response rate (see Table 15).

Table 15. Exploratory Endpoint – Complete Cure (Index+Household; Recommended Imputation)

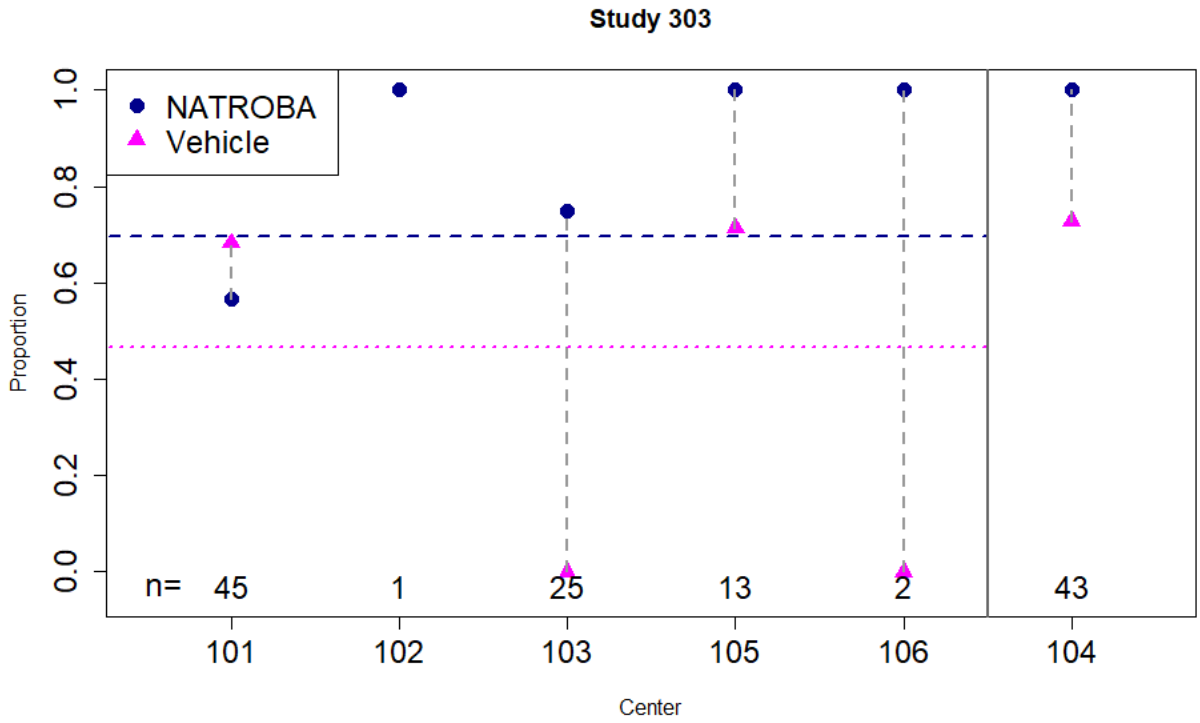
	Study 303		Study 304	
Parameter	**NATROBA N=63 n/N (%)**	**Vehicle N=68 n/N (%)**	**NATROBA N=92 n/N (%)**	**Vehicle N=69 n/N (%)**
Complete cure (index+household)	43/63 (68.3)	25/68 (36.8)	77/92 (83.7)	24/69 (34.8)
Household	13/20 (65.0)	5/25 (20.0)	25/30 (83.3)	4/11 (36.4)
Index	30/43 (69.8)	20/43 (46.5)	52/62 (83.9)	20/58 (34.5)

Source: reviewer analysis

Efficacy by Center

Study 303 enrolled subjects at six sites (including Site 104). Sites 102 (1 subject), 105 (13 subjects) and 106 (2 subjects) were combined into a pooled analyses center for the analyses. Note that the investigator at Site 106 (two subjects) also participated in Study 304 as Site 211 (five subjects). Most of the subjects included in the analyses were enrolled at Sites 101 (45 subjects) and 103 (25 subjects). The treatment effect in Site 101 was in the opposite direction, with more subjects achieving complete cure on the vehicle arm than the NATROBA arm (see Figure 1). The Breslow-Day test for heterogeneity across analysis centers had a p-value of 0.0004, indicating heterogeneity across the analysis centers.

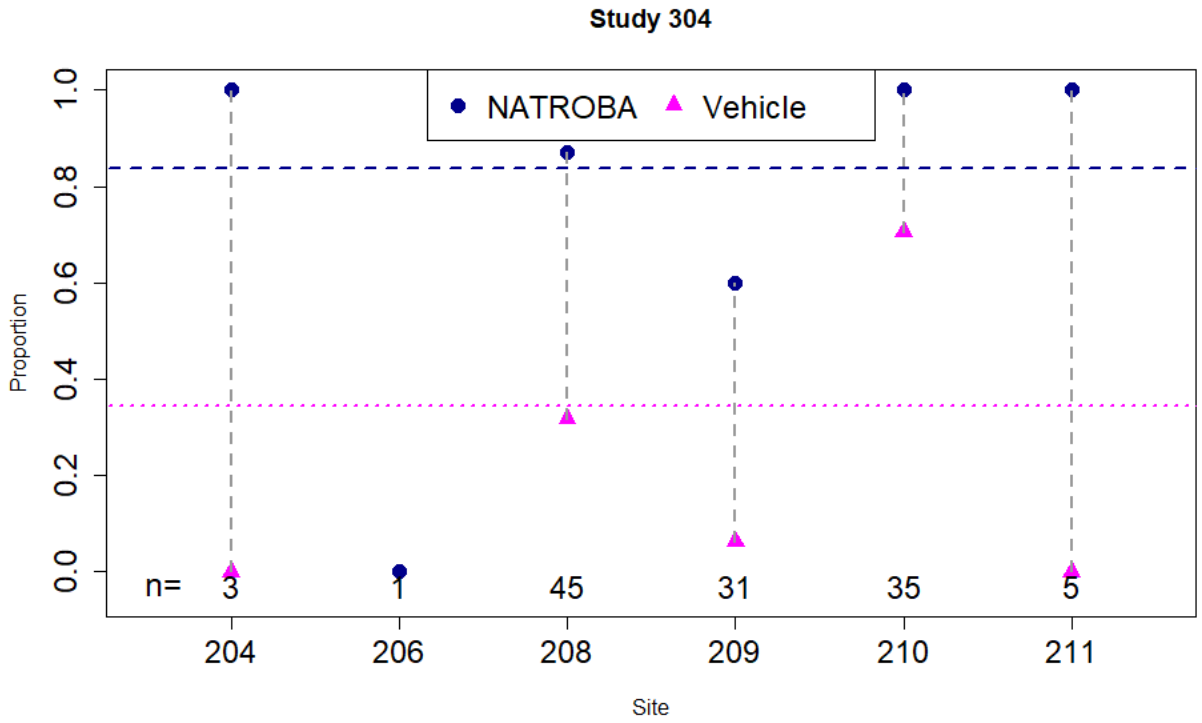
Figure 1. Complete Cure Rate by Site (Study 303; I-ITT)



Source: Reviewer analysis.
Abbreviations: I-ITT, index intent-to-treat; n, total sample size per center

Study 304 enrolled subjects at seven sites (including Site 202). Among the six sites included in the analyses, Sites 204 (three subjects), 206 (one subject), 211 (five subjects) and 209 (31 subjects) were combined into a pooled analyses center for the analyses. Note that the investigator at Site 211 (five subjects) also participated in Study 303 as Site 106 (two subjects). The treatment effects were generally consistent across centers in Study 304 (see Figure 2). The p-value from the Breslow-Day test for heterogeneity across analysis centers was 0.6350, indicating that heterogeneity was not detected.

Figure 2. Complete Cure Rate by Site (Study 304; I-ITT)



Source: Reviewer analysis.
Abbreviations: I-ITT, index intent-to-treat; n, total sample size per center

Site 106 in Study 303 and Site 211 in Study 304 had a common investigator. A sensitivity analysis removing the subjects from these sites (two from Site 106 and 5 from Site 211) was conducted to evaluate the impact of the common investigator. The results from this analysis lead to p-values of 0.043 and <0.001 for assessing the primary endpoint compared to the p-values of 0.0175 and <0.001 for the main analysis using all subjects , for Studies 303 and 304, respectively (see Table 16).

Table 16. Complete Cure at Day 28, Excluding Common Investigator (I-ITT; Recommended Imputation)

	Study 303		Study 304	
Parameter	**NATROBA N=42**	**Vehicle N=42**	**NATROBA N=59**	**Vehicle N=56**
Complete cure (excluding common investigator; recommended imputation), n(%)	29 (69.1)	20 (47.6)	49 (83.1)	20 (35.7)
Treatment difference, %	20.8		47.3	
95% CI	(0.0, 41.9)		(33.2, 61.5)	
P-value	0.043		<0.001	

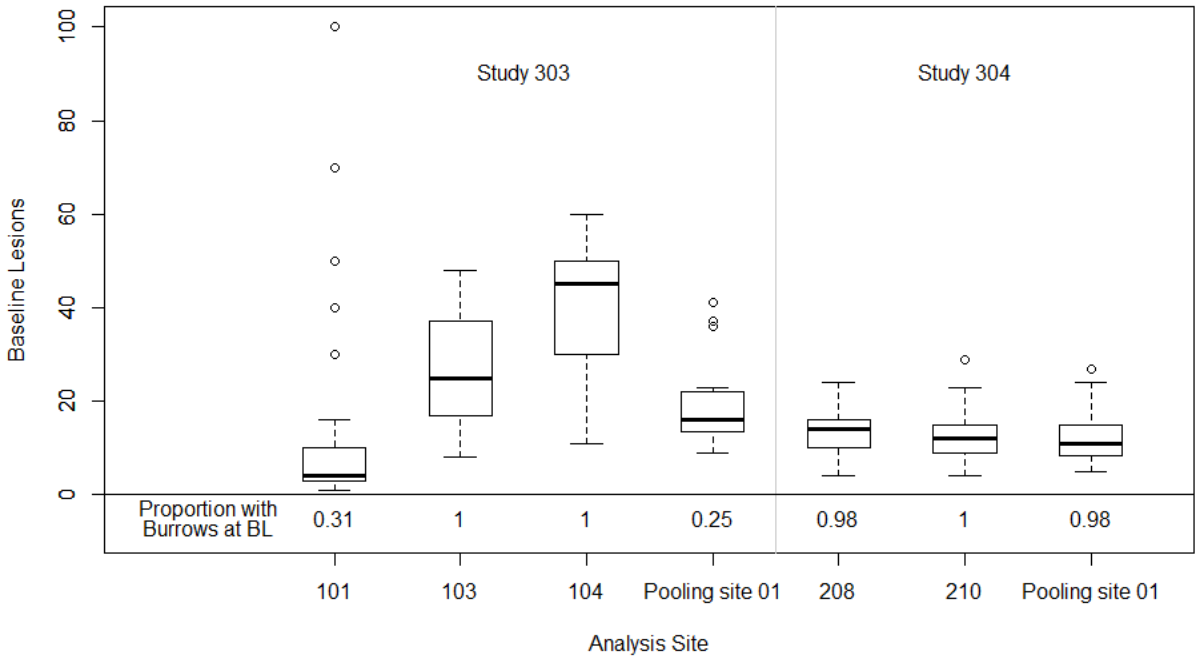
[1]Excluding Site 106 in Study 303 and Site 211 in Study 304; subjects with observed clinical cure but missing microscopic cure imputed as complete cure; subjects with completely missing data imputed as nonresponders
Source: reviewer analysis
Abbreviations: CI, confidence interval; I-ITT, index intent-to-treat

As noted above regarding the baseline characteristics, Studies 303 and 304 differed in the distributions of the number of baseline lesions and the proportion of subjects with evidence of

burrows at baseline. Differences in the distributions were also present among the different sites in Study 303; however, the distributions were similar across sites in Study 304. In particular, Site 101 in Study 303, had many subjects with very few lesions, a few subjects with a large number of lesions, and relatively few subjects with evidence of burrows at baseline, while Sites 103 and 104 had subjects with a moderately large number of lesions and all subjects with evidence of burrows at baseline. Site 105, which was the primary site in Pooled Site 1 in Study 303, also had a relatively low proportion of subjects with burrows at baseline. In Study 304, the distributions of lesions were similar across the sites, and nearly all subjects had evidence of burrows at baseline (see).

Figure 3).

Figure 3. Baseline Disease Severity by Analysis Site (I-ITT)



Source: Reviewer analysis
Abbreviations: BL, baseline; I-ITT, index intent-to-treat

Efficacy by Baseline Severity

In Study 303, about half of the subjects had evidence of burrows at baseline, while nearly all subjects did in Study 304. The protocol defined mild disease as ≤10 lesions at baseline, moderate disease as 11 to 49 lesions, and severe disease as ≥50 lesions. Only a small proportion of subjects had more than 50 lesions at baseline. Study 303 differed from Study 304 in terms of baseline severity, with Study 303 enrolling fewer subjects with burrows at baseline and subjects with a wider range of lesion counts at baseline. The complete cure rates were similar across severity categories in Study 304. However, in Study 303, the lower severity categories at

baseline were associated with higher vehicle response rates and smaller treatment effects (see Table 17).

Table 17. Complete Cure by Baseline Severity (I-ITT; Recommended Imputation)

	Study 303		Study 304	
Parameter	**NATROBA N=43 n/N (%)**	**Vehicle N=43 n/N (%)**	**NATROBA N=62 n/N (%)**	**Vehicle N=58 n/N (%)**
Evidence of burrows				
Yes	13/20 (65.0)	5/23 (21.7)	51/61 (83.6)	19/57 (33.3)
No	17/22 (77.3)	15/20 (75.0)	1/1 (100)	1/1 (100)
Number of lesions				
≤10	15/19 (79.0)	13/20 (65.0)	21/25 (84.0)	7/20 (35.0)
>10	15/23 (65.2)	7/23 (30.4)	31/37 (83.8)	13/38 (34.2)

Source: Reviewer analysis
Abbreviations: I-ITT, index intent-to-treat

Findings in Special/Subgroup Populations

Treatment effects were generally consistent across age, gender, race and ethnicity subgroups, though the studies enrolled relatively few subjects and many of the subgroups were very small (see Table 18).

Table 18. Complete Cure by Subgroup (I-ITT; Recommended Imputation)

	Study 303		Study 304	
Parameter	**NATROBA N=43 n/N (%)**	**Vehicle N=43 n/N (%)**	**NATROBA N=62 n/N (%)**	**Vehicle N=58 n/N (%)**
Age (years)				
4-17 years	5/6 (93.3)	8/12 (66.7)	7/11 (63.6)	1/7 (14.3)
18-64 years	22/33 (66.7)	12/27 (44.4)	38/43 (88.4)	18/48 (37.5)
65+ years	3/4 (75.0)	0/4 (0)	7/8 (87.5)	1/3 (33.3)
Gender				
Female	19/25 (76.0)	11/23 (47.8)	31/34 (91.2)	9/36 (25.0)
Male	11/18 (61.1)	9/20 (45.0)	21/28 (75.0)	11/22 (50.0)
Race				
White	27/39 (69.2)	18/41 (43.9)	35/42 (83.3)	13/38 (34.1)
Black or African-American	3/4 (75.0)	2/2 (100)	12/15 (80.0)	4/12 (33.3)
Other	--	--	1/1 (100)	0/2 (0)
Asian	--	--	4/4 (100)	1/4 (25.0)
Native HI/Pacific Islander	--	--	--	2/2 (100)
Ethnicity				
Not Hispanic or Latino	8/13 (61.5)	8/13 (61.5)	31/35 (88.6)	11/30 (36.7)
Hispanic or Latino	22/30 (73.3)	12/30 (40.0)	21/27 (77.8)	9/28 (32.1)

Source: Reviewer analysis.
Abbreviations: I-ITT, index intent-to-treat; HI, Hawaiian

Data Quality and Integrity

Both Studies 303 and 304 had data quality and integrity issues identified by the Applicant and discussed in the submission. The data from one site of each study was removed from the analyses by the Applicant due to integrity issues. The data from Site 104 was removed from the

analysis of Study 303 because the investigator was indicted for conspiracy to commit wire and mail fraud, fraudulently obtaining controlled substances, and furnishing false information to the U.S. Drug Enforcement Administration related to actions in a different clinical trial. The data from subjects enrolled at Site 104 are not included in the efficacy or safety analyses, but are included in certain sensitivity analyses. The removal of Site 104 from the efficacy analyses had a significant impact on the outcome because Site 104 enrolled approximately one-third of the index subjects in the study.

In Study 304, the investigator at Site 202 did not comply with randomization procedures. While 18 subjects were enrolled at this center (9 index subjects randomized to NATROBA and 9 index subjects randomized to vehicle with no household subjects), all subjects were treated with vehicle. The issue was identified during the study and the Applicant terminated the site. The 18 subjects from Site 202 were excluded from efficacy analyses but included in safety analyses (as treated).

8.1.3. Assessment of Efficacy Across Studies

Studies 303 and 304 were conducted under identical protocols and had the same design and endpoints. The inclusion criteria were the same for both trials, defining an index subject as the youngest member in a household (≥4 years of age) with an active scabies infestation. An active scabies infestation was defined as the presence of clinical signs and symptoms (evidence of burrows or scabies lesions and pruritus) as well as microscopic evidence from a skin scraping or dermatoscopy to demonstrate the presence of mites, eggs, and/or scybala. However, while nearly all subjects in Study 304 had burrows at baseline, only half of the subjects in Study 303 did. In addition, the subjects enrolled in Study 303 had a wider range of lesions present at baseline than subjects enrolled in Study 304. The proportion of subjects with burrows and median number of baseline lesions varied across centers in Study 303, but was more consistent in Study 304.

Primary Endpoints

Although the statistical significance in Study 304 for the primary endpoint of complete cure at Day 28 was clearly demonstrated ($p<0.001$), the results from Study 303 were more difficult to interpret. In Study 304, the results were consistent across centers and subgroups, and the impact of missing data on the conclusions was minimal. On the other hand, the study results in Study 303 were significantly affected by the decision to remove one-third of the index subjects from the analysis from Site 104, substantially reducing the power of the study to demonstrate a significant treatment effect.

Complete cure rates in Study 303 varied across centers and by measures of baseline severity. Due to the smaller sample size, the handling of missing data also had a greater impact on the interpretation of results in Study 303. Although only one subject did not have any end-of-study assessments, four subjects had end-of-study assessments for clinical cure but did not have skin scrapings taken to assess microscopic cure. In the Applicant's study report, all subjects with partial or completely missing data at Day 28 were removed from the analysis. The Applicant's

complete case analysis and an analysis that imputes all subjects with partial missing data at Day 28 as nonresponders lead to analyses that do not meet the statistical significance criterion (p=0.059 and p=0.1946, respectively). However, while skin scrapings for microscopic assessments may be useful for confirming a scabies diagnosis at baseline, they were less useful for confirming that subjects with clinical cure (i.e., no lesions, pruritus, or burrows) were free of mites, eggs, and/or scybala. For all subjects with clinical cure and for whom a microscopic assessment was conducted, the microscopic assessment had negative findings (i.e., the combination of clinical cure and positive microscopy was never observed in any subject in the studies). Thus, it is reasonable to treat subjects with observed clinical cure at Day 28 as achieving complete cure rather than as nonresponders. In the analysis that treats subjects with observed clinical cure but missing microscopic assessment as achieving complete cure, Study 303 met the statistical significance criterion (p=0.0175). The results of this analysis are summarized in Table 19. Thus, both Studies 303 and 304 support the efficacy of NATROBA in the treatment of scabies.

Table 19. Complete Cure at Day 28 (I-ITT; Recommended Imputation)

	Study 303		Study 304	
Parameter	**NATROBA N=43**	**Vehicle N=43**	**NATROBA N=62**	**Vehicle N=58**
Complete cure (recommended imputation)[1], n (%)	30 (69.8)	20 (46.5)	52 (83.9)	20 (34.5)
Treatment difference, %	22.7		49.7	
95% CI	(1.8, 43.5)		(36.0, 63.5)	
P-value	0.0175		<0.001	

[1]Subjects with observed clinical cure but missing microscopic cure imputed as complete cure; subjects with completely missing data imputed as nonresponders
Source: reviewer analysis

Abbreviations: I-ITT, index intent-to-treat; CI, confidence interval

Subpopulations

Treatment effects were generally consistent across age, gender, race, and ethnicity subgroups, though the studies enrolled relatively few subjects and many of the subgroups, especially the racial subgroups, were very small.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety of NATROBA (spinosad) topical solution, 0.9% focused on data from the POC Study (SPN-401-12) and two Phase 3 studies, Study 303 and Study 304. Data from these three studies were pooled together to compare incidences of AEs. These studies were chosen as the focus of the safety review because of the similarity of design, the homogeneous population, NATROBA dose, dosing regimen, and duration of treatment reflects anticipated use. The obtained data allowed the direct comparison of AE rates in NATROBA-treated subjects to vehicle-treated subjects.

The Applicant provided pooled data analyses using the following strategy:

- Pool A: Proof of Concept Study SPN-401-12 (21 subjects)
- Pool B: Study 303 and Study 304 (571 subjects)
- Pool C: Studies SPN-401-12, Study 303, and Study 304 (592 subjects)

For our safety review, the safety population included all subjects in the Proof-of-Concept study and both Phase 3 studies who received at least one application of NATROBA and were evaluated subsequent to removal of the drug.

To determine the safety profile of NATROBA (spinosad) topical solution, 0.9%, the review team analyzed the following types of pooled data: Exposure, demographics, treatment-emergent adverse events (TEAEs), local skin reactions (LSRs), SAEs, AEs leading to discontinuation, clinical laboratory findings, and vital signs.

8.2.2. Review of the Safety Database

Overall Exposure

The safety analysis set (safety population) included all study subjects who received at least one study drug application and completed the study. Across all three studies (Pool C), a total of 592 subjects received the study drug, 322 (54.4%) received NATROBA and 270 (45.6%) received vehicle. Exposure was determined by weighing the patient's tube before and after one application.

Because the total dosing was a single drug application, the extent of exposure is evaluated by determining the mean amount of study drug used (in grams) in each treatment arm. The two Phase 3 Studies (Pool B, Study 303 and Study 304) were the only studies in which the extent of study drug exposure was measured. Out of a total of 571 subjects (96.5% of the safety population), 306 (53.6%) received NATROBA, and 265 (46.4%) received vehicle. The overall exposure for Pool B subjects is summarized in the following table:

Table 20. Extent of Exposure in Pool B

	Study 303			Study 304	
Parameter	**NATROBA (Primary) N=141**	**Vehicle (Primary) N=130**	**NATROBA (PK) N=20**	**NATROBA N=145**	**Vehicle N=135**
Mean amount of study drug used (in grams) (SD)	59.06 (26.52)	60.58 (21.11)	38.31 (27.13)	70.32 (27.67)	71.49 (23.89)

Source: Reviewer
Abbreviations: PK, pharmacokinetics; SD, standard deviation

Reviewer comment: The amount of NATROBA used by subjects in the PK sub-study compared to the amount used by subjects in the rest of Study 303 and Study 304 is less because the study population of the PK subset consisted of pediatric subjects 5 to 16 years of age who have smaller body surface areas compared to adults.

Adequacy of the Safety Database

The number of subjects exposed to the study drug (592) and the amount of product used for treatment is sufficient to characterize the safety of NATROBA (spinosad) topical suspension, 0.9% in the treatment of scabies.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of NATROBA (spinosad) topical suspension, 0.9% for the treatment of scabies. However, based on a general advice letter from the FDA expressing concerns about study violations that occurred at Site 104 in Study 303, the Applicant excluded data from 73 subjects who were treated at the site (65 subjects in the double-blind, randomized portion of the study and 8 subjects in the PK study).

Categorization of Adverse Events

For the safety analysis set, the Applicant defined an AE as "any untoward medical occurrence in a subject or clinical investigation (lab assay, physical change, etc.) following the subject's first dose of investigative product (IP) that does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable or unintended sign (including an abnormal finding on lab assays, vital signs, etc.), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP. This includes any adverse occurrence that is new in onset or aggravated in severity, duration or frequency from the baseline condition (including the physical examination), or abnormal results of diagnostic procedures (including laboratory test abnormalities)." Of note, an AE will not include "[a]bnormal laboratory findings or test results (unless considered clinically significant in the opinion of the investigator or specifically defined elsewhere in the protocol) related to the disease being studied (unless more severe than expected)."

AEs were categorized by system-organ class and preferred term using the Medical Dictionary for Regulatory Activities version 20.0. The coding of AEs in the NDA submission appeared adequate and allowed for accurate estimation of AE risk.

An SAE was defined as an AE that met any of the following criteria:

- Resulted in death.
- Was life-threatening.
- Required hospitalization or a prolongation of an existing hospitalization.
- Persistently or significantly incapacitated or substantially disrupted the ability to conduct normal life functions.
- Resulted in a congenital anomaly or birth defect.

- Was considered as any other important medical event that may not result in death, be life-threatening, or require hospitalization, but still may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed in this definition.

The investigator was responsible for performing periodic and special assessments for AEs. AE collection began once the drug was first administered and continued until the end of study visit was complete. All AEs were reported, regardless of whether or not they were deemed to be related to the IP. Investigators categorized AEs by seriousness, severity, causality, action taken with the study drug, and the outcome.

The investigator assessed severity for each AE and SAE reported during the study. The severity of each AE and SAE was assigned a classification of mild, moderate, or severe and recorded on the AE case report form. Skin and eye assessments were to document presence or absence of irritation. Eye irritation was rated based on the severity ratings in the Site Eye Irritation Guide.

The investigator assessed the relationship between study product and the occurrence of each AE or SAE and categorized the potential relationship as follows:

- Related: There is a possible temporal and/or causal relationship to the IP.
- Not related: There is no temporal and/or causal relationship to the IP.

Investigators followed unrelated AEs until the final study visit (Day 28). All SAEs and AEs deemed by the investigator to be related to IP or treatment, were followed until the AE had resolved.

SAEs occurring during the studies were reported to a clinical research organization (CRO) on a Serious Adverse Event report form via fax within 24 hours after the time the investigator became aware of the SAE. The CRO would then notify the IRB within 1 week. The investigator would continue to provide follow-up information to the CRO as it became available.

The Applicant presented standard AE analyses. The definition of AE and SAE are acceptable. The classification system used by investigators to describe the severity of AEs as well as the causal relationship between AEs and study product are also acceptable.

Routine Clinical Tests

Routine safety monitoring at screening, the first (application) visit, and end of study visit included: vital signs (weight, blood pressure, and heart rate), a general skin assessment (including eye), clinical laboratory evaluations (only in Study 303; complete blood count, chemistry, urine pregnancy test as applicable), concomitant medications, and AEs. Only an abbreviated skin/eye assessment and AEs were performed on the second day visit. Only concomitant medications and AEs were performed on the 14-day telephone visit. No electrocardiograms (ECGs) were performed during the studies because of the negligible systemic exposure.

Overall, safety monitoring performed during the conduct of studies supporting this NDA was appropriate and adequate for evaluation of the safety of NATROBA.

8.2.4. Safety Results

Deaths

There were no deaths during the development program for NATROBA (spinosad).

Serious Adverse Events

In the safety population (Pool C), no subjects treated with NATROBA experienced SAEs. In Study 303, two subjects, both in the vehicle group, experienced SAEs. One subject experienced SAEs of acute kidney injury, anemia, esophageal varices, gastrointestinal hemorrhage, and hyponatremia. All but the anemia resolved during the study. The other vehicle subject experienced an SAE of cellulitis, which resolved during the study.

Dropouts and/or Discontinuations Due to Adverse Effects

No subjects in the safety population discontinued due to AEs. Of the 592 subjects in the safety population, 23 (3.9%) subjects failed to complete the study. The reasons given for discontinuation were Other (4 (0.7%)), Lost to Follow-Up (16 (2.7%)), and Withdrawal by Subject (3 (0.5%)). Nonetheless, all 592 subjects were evaluated for AEs at the Day 2 visit and thus included in the safety analyses. None of these subjects experienced TEAEs.

Significant Adverse Events

No other significant AEs were reported during the conduct of studies that support this application.

Treatment-Emergent Adverse Events and Adverse Reactions

Common Adverse Events

There were 70 TEAEs reported in 48 subjects. TEAEs were reported in 31 subjects receiving NATROBA (9.6% in Pool C) and in 17 subjects receiving vehicle (6.3% in Pool C).

The table below summarizes TEAEs by preferred term that occurred frequently in the safety population and highlights that the most common TEAEs were LSRs, occurring at the application site.

Table 21. TEAEs by Preferred Term in >1% of Subjects Across All Pools

	Pool A		Pool B		Pool C	
	SPN-401-12 N=21		Study 303 (+PK) and Study 304 N=571		SPN-401-12, Study 303, Study 304 N=592	
Preferred Term	NATROBA N=16 n(%)	Vehicle N=5 n(%)	NATROBA N=286 n(%)	Vehicle N=265 n(%)	NATROBA N=322 n(%)	Vehicle N=270 n(%)
Application site irritation[a]	6 (37.5)	0	2 (0.7)	0	8 (2.6)	0
Dry skin	5 (31.3)	0	1 (0.3)	0	6 (2.1)	0
Headache[b]	0	1 (20)	2 (0.7)	2 (0.8)	2 (0.7)	3 (1.1)
Erythema[b]	1 (6.3)	0	0	1 (0.4)	1 (0.3)	1 (0.4)
Application site anesthesia[b]	1 (6.3)	0	0	0	1 (0.3)	0
Nasopharyngitis[b]	1 (6.3)	0	0	0	1 (0.3)	0
Animal scratch[b]	1 (6.3)	0	0	0	1 (0.3)	0
Procedural pain[b]	1 (6.3)	0	0	0	1 (0.3)	0
Application site paresthesia[b]	0	1 (20)	0	0	0	1 (0.4)
Arthropod bite[b]	0	1 (20)	0	0	0	1 (0.4)
Concussion[b]	0	1 (20)	0	0	0	1 (0.4)
Excoriation[b]	0	1 (20)	0	0	0	1 (0.4)
Laceration[b]	0	1 (20)	0	0	0	1 (0.4)
Ligament sprain[b]	0	1 (20)	0	0	0	1 (0.4)

Source: Reviewer
[a] "Application site irritation", "burning sensation" or "application site pain" were also coded with a PT of "application site irritation."
[b] All TEAEs with these preferred terms were considered unrelated to treatment
Abbreviations: PK, pharmacokinetics; PT, preferred term; TEAE, treatment-emergent adverse event

Reviewer comment: The safety analysis identified that all TEAEs related to study drug administration occurring in at least 1% of subjects were LSRs.

Adverse Reactions

Based on the topical route of administration of NATROBA over a large body surface area, LSRs were considered adverse events of special interest. Although the drug was applied to a large body surface area, the number of subjects experiencing local skin reactions was relatively low. The most frequent adverse reactions were application site irritation (to include burning sensation and application site pain) and dry skin, occurring only in NATROBA-treated subjects and notably absent in subjects using vehicle. All adverse reactions were mild in severity. Only one pediatric subject experienced an adverse reaction (burning sensation). No subjects participating in the PK subset (Study 303) experienced adverse reactions (though per protocol, their skin was not assessed after the 12-hour post study drug application).

No subjects experienced eye irritation with NATROBA or vehicle application.

Table 22. Local Skin Reactions by Frequency (≥1%) and by Preferred Term

	Pool A		Pool B		Pool C	
	SPN-401-12 N-21		Study 303, Study 304 N=571		SPN-401-12, Study 303, Study 304 N=592	
Preferred Term	NATROBA N=16 n(%)	Vehicle N=5 n(%)	NATROBA N=306 n(%)	Vehicle N=265 n(%)	NATROBA N=322 n(%)	Vehicle N=270 n(%)
Application site irritation[a]	6 (37.5)	0	2 (0.7)	0	8 (2.5)	0
Dry skin	5 (31.3)	0	1 (0.3)	0	6 (1.9)	0

Source: Reviewer
[a] "Burning sensation" or "application site pain" were also coded with a PT of "application site irritation"
Abbreviations: PT, preferred term

Laboratory Findings

Clinical laboratory evaluations were only conducted during Study 303, including the PK study (161 NATROBA subjects, 130 vehicle subjects). Two NATROBA subjects (1.2%) and three (2.3%) vehicle subjects had clinical laboratory abnormalities. None of these laboratory evaluations were considered by the investigator to be related to the study drug or clinically relevant.

Vital Signs

No clinically significant vital sign abnormalities were reported in the NATROBA (spinosad) group.

ECGs

No ECGs were performed during the development program for NATROBA (spinosad) because of the negligible systemic exposure.

QT

The Applicant did not conduct a QT study during the studies. In the original submission for head lice, a QT/IRT review in 2011 determined that "If…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 (…)." According to the MUsT results (Study 303 PK bioavailability study under maximal usage conditions) in 19 pediatric subjects 5 to 16 years of age, the systemic exposure for spinosyn A and spinosyn D was not quantifiable, and limited systemic exposure for benzyl alcohol up to 12-hours post-treatment, which demonstrates similar bioavailability as what was observed in the studies in the original submission.

Immunogenicity

This section of the review is not applicable to this product.

8.2.5. Analysis of Submission-Specific Safety Issues

Refer to Section 8.2.4 for discussion of LSRs.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

No clinical outcome assessment analyses informing safety or tolerability was performed as part of the safety review.

8.2.7. Safety Analyses by Demographic Subgroups

In the safety population, subjects had a mean age of 31.6 years in the NATROBA group and 37.4 years in the vehicle group. Subjects were female (52.2% in NATROBA group and 57% in the vehicle group) and were mostly Caucasian (83.9% NATROBA, 87% vehicle).

The safety of NATROBA was assessed for each study, as well as for pooled data (Pool A, Pool B, and Pool C) by subgroups of: gender, race, age, and ethnicity.

Scabies presents in a similar manner across racial and ethnic subgroups, so subjects who were included in NATROBA efficacy and safety data appear generally representative of the population of patients with scabies that are expected to be treated with NATROBA in the United States.

Gender

The overall incidence of adverse reactions was slightly higher in females treated with NATROBA (2% for irritation, 1.7% for dry skin) than males taking NATROBA (0.7% and 0.3% respectively) in all three studies. Nonetheless, no safety signals emerged from individual studies or from the integrated data from Pools A, B, and C when analysis of AEs by gender was conducted.

Race

Two of the dry skin reactions were experienced by whites (0.7%) and two nonwhite races (African American, Asian, 0.1% each). Irritation was experienced by six whites (2%), two nonwhites (both Asian). Because of the small number of non-Caucasian subjects, no meaningful conclusion could be drawn with regard to LSR and race. Even with these differences, race-dependent safety signals were not evident during the safety analysis of NATROBA.

Ethnicity

Both irritation and dry skin were each experienced by similar rates of Hispanics and non-Hispanics (four each, 1.3%). No ethnic-dependent safety signals were evident during the safety analysis of NATROBA.

Age

Of the adverse reactions related to NATROBA, only one was experienced by a pediatric patient (burning sensation). Because of the small number of non-Caucasian subjects, no meaningful conclusion could be drawn with regard to LSR and race. Even with these differences, race-dependent safety signals were not evident during the safety analysis of NATROBA.

8.2.8. Specific Safety Studies/Clinical Studies

The Applicant did not conduct additional specific studies or clinical trials to evaluate a potential safety concern as part of the development program.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No specific carcinogenic studies were conducted.

Human Reproduction and Pregnancy

No specific studies of pregnancy or lactation were conducted. There were no pregnancies reported during the development of NATROBA.

Subjects were not eligible to enroll in the NATROBA development program if they were pregnant, breastfeeding, sexually active, or may become sexually active and were unwilling to practice responsible birth control methods (e.g., combination of condoms and foam, birth control pills, intrauterine device, patch, shot or vaginal ring, etc.).

Female subjects who had reached menarche were required to have a negative urine pregnancy test prior to treatment with study drug.

Pediatrics and Assessment of Effects on Growth

The effects of NATROBA on growth were not evaluated. Because the treatment with NATROBA, 0.9% consists of a single application, it is reasonable to conclude that it is unlikely that NATROBA would have an effect on growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Considering the mechanism of action of NATROBA, it is reasonable to conclude that there is no risk for abuse potential, withdrawal, or rebound effects.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

NATROBA (spinosad) topical suspension, 0.9% is approved in the United States for the indication of head lice in patients 6 months of age and older. Since the original approval in 2011, there have been no newly-identified safety signals.

Expectations on Safety in the Postmarket Setting

The safety profile of NATROBA for the treatment of scabies is similar to NATROBA for the treatment of head lice, thus we expect there will be no increased risk of NATROBA in the postmarketing setting.

8.2.11. Integrated Assessment of Safety

The safety profile for NATROBA (spinosad) topical suspension, 0.9% in the treatment of scabies was adequately characterized during the development program. The primary safety database consisted of 592 subjects from Studies SPN-401-12, Study 303, and Study 304.

There were no deaths in the development program for NATROBA. No subject who received NATROBA experienced an SAE. The most frequent adverse reactions were application site irritation (to include burning sensation and application site pain) and dry skin.

8.3. Statistical Issues

The results of Study 304 were consistent across centers and subgroups and the impact of missing data on the conclusions was minimal. The key statistical issue in Study 304 was that the Applicant did not follow the prespecified method for handling missing data and presented an observed-case analysis rather than accounting for all subjects in the analysis, though the handling of missing data did not impact the overall conclusions.

On the other hand, the results from Study 303 were more difficult to interpret. The key statistical issues in Study 303 included:

- The impact of the Applicant's decision to remove the data from the analysis from Site 104. The removal of subjects from this site reduced the sample size for the index subjects by one-third, substantially reducing the power of the study to demonstrate a significant effect.
- Complete cure rates in Study 303 varied across centers and by measures of baseline severity.
- As with Study 304, the Applicant did not follow the prespecified method for handling missing data and presented an observed case analysis rather than accounting for all subjects in the analysis. Due to the smaller sample size, the handling of missing data also had a greater impact on the interpretation of results in Study 303. The reviewer

recommends following the protocol-specified methods for subjects who did not attend the Day 28/end-of-study visit.

- An additional complication was related to subjects who attended the Day 28 visit and were assessed for clinical cure but did not consent to skin scrapings for the microscopic assessment. After careful assessment of the relationship between clinical cure and microscopic cure, the reviewer noted that all subjects in Studies 303 and 304 who achieved clinical cure also achieved microscopic cure. Thus, an assessment of clinical cure is sufficient for determining that a subject met the complete cure criteria. The reviewer recommends imputing subjects with observed clinical cure but missing the microscopic assessment at Day 28 as having achieved complete cure.

After assessing the impact of these statistical issues on the study findings, the reviewer concluded that the totality of evidence from Studies 303 and 304 supports the efficacy of NATROBA in the treatment of scabies.

8.4. Conclusions and Recommendations

To establish the effectiveness of NATROBA (spinosad) topical suspension, 0.9% in the treatment of scabies, the Applicant submitted results from two randomized, two-arm, vehicle-controlled, multicenter Phase 3 trials (Study 303 and Study 304). The trials enrolled 551 subjects 4 years of age and older diagnosed with scabies infestation by clinical and microscopic/dermatoscopic evaluation.

In these two Phase 3 trials, index subjects were randomized in a 1:1 ratio (along with their household members) to receive NATROBA or vehicle as a single application. Subjects applied the study drug from the neck down to the soles of the feet, leaving it on for a minimum of 6 hours before showering or bathing.

The primary efficacy endpoint was the percentage of index subjects with complete cure of scabies at Day 28. Complete cure was defined as both clinical and dermatoscopic/microscopic cure, including the absence of all clinical signs and symptoms of scabies with a negative microscopy and dermatoscopy. The two studies support the efficacy of NATROBA in the treatment of scabies in patients 4 years of age and older.

The Applicant conducted a comprehensive assessment of the safety of NATROBA (spinosad) topical suspension, 0.9% in patients 4 years of age and older. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

At this time, inspection of clinical sites is delayed due to travel restrictions and prioritization of mission-critical site inspections due to the COVID-19 pandemic. Pending successful preapproval inspection, the submitted safety and efficacy data support approval of this NDA for NATROBA (spinosad) topical suspension, 0.9% in patients 4 years of age and older for the treatment of scabies.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee was held for this NDA because the application did not raise significant safety or efficacy issues in the intended population.

10. Pediatrics

The Applicant submitted an Initial Pediatric Study Plan (iPSP) on July 26, 2015 which included a request for a partial waiver from conducting clinical trials in the pediatric population from 0 to (b) (4) of age.

On February 15, 2016, the FDA communicated an agreed iPSP to the Applicant with the following:

- PK study for subjects 4 years of age and older to be conducted prior to submission of NDA/efficacy supplement,
- A partial waiver from conducting studies in pediatric patients 0 to 6 months of age due to safety concerns about benzyl alcohol (BA) and its metabolites causing gasping syndrome in this populations
- An adequate juvenile animal toxicity study to be conducted to support clinical trials in pediatric subjects 6 months to 4 years of age
- Deferral of clinical trials in pediatric subjects 6 months to 4 years of age

The Applicant completed a PK evaluation in subjects 4 years of age and older as a part of a Phase 3 trial (Study 303).

The Applicant conducted two Phase 3 studies that included pediatric subjects with scabies infestation 4 to 18 years of age. Additional studies in pediatric subjects 1 month to <4 years of age will be conducted during postmarketing as part of the Pediatric Research Equity Act postmarketing requirement (PMR) (see Section 13).

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton/container labels for NATROBA (spinosad) topical suspension, 0.9%. The review team provided recommendations regarding PI which are provided throughout this review. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis reviewed the proposed PI, PPI and the carton and container labels for NATROBA (spinosad) topical suspension, 0.9% and provided comments. The Division concluded that the PI and PPI were acceptable from a medication error perspective and that the container labels and carton labeling can be improved to remove inconsistencies between the PI and the carton labeling and to facilitate product identification. (See reviews dated September 18, 2020 and September 22, 2020). The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI, and carton/container labeling. Refer to the DMPP/OPDP review by Ruth Mayrosh, PharmD and Laurie Buonaccorsi, PharmD, dated October 29, 2020. These comments are reflected in final labeling. Table 25 provides the location of the labeling discussion for each section.

Table 233: Location of the Labeling Discussion for Significant High-Level Labeling Changes

Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Section 1.1
2 DOSAGE AND ADMINISTRATION	Section 6.2.2
5 WARNINGS AND PRECAUTIONS	Sections 8.2.4, 8.2.5, 8.2.11
6 ADVERSE REACTIONS	Section 8.2.4
12 CLINICAL PHARMACOLOGY	Sections 6.2.1, 6.3.1
14 CLINICAL STUDIES	Section 8.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling

11.2 Patient Labeling

The Applicant submitted a proposed patient package insert (PPI) for NATROBA (spinosad) topical suspension, 0.9%. The Division of Medical Policy Programs and OPDP reviewed and provided comments regarding the PPI. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Ruth Mayrosh, PharmD and Laurie Buonaccorsi, PharmD dated October 29, 2020.

12. Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies are recommended.

13. Postmarketing Requirements and Commitment

Per the agreed iPSP on February 15, 2016, the Applicant will conduct postmarketing trials as follows:

- An adequate juvenile animal toxicity study and PK study conducted to support clinical trials in pediatric subjects 6 months to 4 years of age, and
- Deferral for clinical trials in pediatric subjects 6 months to 4 years of age.

In 2019, DPMH and DCaRP (now DCN) were consulted to comment on the permissible levels of excipients, including BA, in product formulations for pediatric patients. Following review of literature DPMH concluded the following:

"Published reports of BA toxicity resulting in the clinical pattern of multi-organ dysfunction, coined "the gasping syndrome", have been almost exclusively described in very low birth weight preterm neonates and nearly all have described a fatal outcome. This reviewer identified no publications describing benzyl alcohol toxicity outside of the neonatal setting, but the potential for BA toxicity in older pediatric patients remains a theoretical possibility."

In addition, it was concluded that "there is no strong evidence to justify contraindication to the use of benzyl alcohol as an excipient in products intended for pediatric use."

On the basis of this review, DPMH recommended that studies in pediatric patients 1 month to <4 years of age be conducted as a PMR. Studies in pediatric patients 0 to <1 month of age can be partially waived because studies in this age group would be impossible or highly impracticable.

DDD agreed with DPMH's recommendations for partial waiver from conducting studies in pediatric subjects 0 to <1 month of age and requiring a study in 100 pediatric subjects with scabies 1 month to <4 years of age. This study will include at least 16 subjects for PK evaluation under maximal use conditions. This proposal was presented at the Pediatric Review Committee on November 10, 2020. The PeRC agreed with the DDD recommendation.

Based on the challenges of conducting studies during the COVID-19 pandemic, the Applicant requested enrollment of fewer subjects and a longer period to conduct the study. Thus, the following PMR will be issued:

Conduct a pediatric PK and safety study in pediatric subjects 1 month to 3 years 11 months of age with a total of 50 pediatric subjects with scabies infestation being enrolled, with a minimum of 16 completers in the PK evaluation, and with adequate number of subjects within the lowest age range.

The timeline will be as follows:

- Final Protocol Submission: 04/2021

- Study Completion: 10/2022
- Final Report Submission: 02/2023

14. Appendices

14.1. References

Centers for Disease Control and Prevention, 2019, Scabies: Medications, accessed, https://www.cdc.gov/parasites/scabies/health_professionals/meds.html.

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Olta Pharmaceuticals Corporation, Morton Grove Pharmaceuticals, Inc., and VersaPharm Incorporated, 2003, Lindane Lotion/Shampoo USP, 1%, https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/006309lotionlbl.pdf.

U.S. Food and Drug Administration, 2015, FDA Public Health Advisory: Safety of Topical Lindane Products for the Treatment of Scabies and Lice, https://wayback.archive-it.org/7993/20170722191412/https:/www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110845.htm.

14.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and subinvestigators who participated in covered clinical studies for NATROBA (spinosad) topical suspension, 0.9%. Prior to study initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were studies SPN-401-12, SPN-303-15 (Study 303), and SPN-304-15 (Study 304), which provided the primary data to establish effectiveness and safety of this product.

The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Covered Clinical Study (Name and/or Number): SPN-401-12

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 8		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): SPN-303-15

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 18		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): SPN-304-15

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 24		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

Not applicable.

14.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

14.4.1. Individual Study Summary

This supplemental new drug application (sNDA) consists of three studies: A Phase 2 (Note: The Applicant defined this study as Phase 4) proof-of-concept (POC) study (SPN-401-12) and two similarly designed pivotal Phase 3 safety and efficacy studies (Study 303 and Study 304). A single pharmacokinetics (PK) study was conducted as part of Study 303 in the treatment of scabies infestations.

The Phase 3 studies were identical in design, with the exception that only Study 303 included PK and clinical laboratory evaluations and was conducted in two parts: a PK study and a primary study. The PK study and the primary study followed different designs and included different subject populations. Specifically, the PK study evaluated PK and safety in a set of subjects, all of whom received NATROBA and were evaluated over a 12-hour post-treatment period. The primary study was, with the exception of the collection of clinical laboratory evaluations, identical in design to Study 304. In the primary study, as in Study 304, subjects were randomized to receive either NATROBA or vehicle, and were assessed for efficacy and safety over a 28-day post-treatment follow-up period.

Clinical Pharmacology review focuses on the bioavailability assessment of NATROBA (spinosad) topical suspension, 0.9%.

14.4.2. Study 303

Study Title:

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Efficacy and Pharmacokinetics of NATROBA™ (spinosad) for the Treatment of Scabies

Methods:

This study included 2 separate parts, referred to as the primary study and the PK study.

The primary study was a multicenter, randomized, double-blind, two-arm, vehicle-controlled, 28-day evaluation of the safety and efficacy of a single application of NATROBA in comparison with vehicle for the treatment of scabies in subjects 4 years of age or older.

The PK study was a multicenter, open-label determination of the PK characteristics of NATROBA (i.e., spinosad and benzyl alcohol) over the first 12 hours after study drug application in a separate pediatric population of subjects 4 to 16 years of age.

Primary Study:

Approximately 120 index subjects were randomized in a 1:1 ratio to apply a single topical dose of either NATROBA or vehicle. All subjects were evaluated at three study visits: Day 1 (screening, randomization, and treatment), Day 2, and Day 28 (or early termination). Additionally, all subjects received a well-being telephone call on Day 14.

After randomization on Day 1, the subjects were dispensed study drug (NATROBA or vehicle) to apply at home later the same day as a single treatment over the entire body from the neck down to the toes (including the soles of the feet) and to the scalp (if balding) or hairline, temples, and forehead. Subjects were instructed to rub the treatment into the skin followed by a 10-minute waiting period before getting dressed. Subjects were further instructed to shower or bathe no earlier than 6 hours after study drug application and at least 1 hour prior to the Day 2 visit.

Pharmacokinetic Study:

Approximately 24 unique pediatric subjects (i.e., subjects who did not reside in the index subject's households and were not part of the primary study) participated in the PK study. The PK study was planned to include approximately 12 male or female subjects 4 to 9 years of age, with approximately six male or female subjects 4 to 6 years of age and 12 male or female subjects 10 to 16 years of age.

For subjects in the PK study, NATROBA was applied at the study center during a single visit with assistance from a caregiver using the same instructions and following the same restrictions regarding dressing and bathing as described for the primary study. Blood samples were collected at 0 hours (just prior to study drug application), and then at 0.5, 1.0, 3.0, 6.0, and 12 hours postapplication. The subjects remained at the study center until the 12-hour procedures were completed. Bathing must have occurred after the 6-hour blood draw but prior to the 12-hour blood draw.

No efficacy evaluations were included in the PK study. Safety evaluations included monitoring of adverse events (AEs), assessments of general skin and eye irritation, analyses of clinical laboratory parameters, and measurements of vital signs.

Duration of Treatment:

All subjects (primary study and PK study) received a single topical application of study drug.

Criteria for Evaluation: Efficacy (Primary Study Only):

The primary efficacy endpoint was as follows:

- The percentage of index subjects with complete cure of scabies at Day 28

The exploratory efficacy endpoints included the following:

- The percentage of subjects with clinical cure at Day 28
- The percentage of subjects with microscopic cure at Day 28
- The number of new lesions at Day 28
- The change from baseline in total lesion counts at Day 28
- The percentage of subjects in the intent-to-treat (ITT) population who were infested at baseline and had complete cure at Day 28

Pharmacokinetics (Pharmacokinetic Study Only):

Analysis of the PK variables was considered a secondary endpoint in this study, and included plasma concentrations of spinosyn A, spinosyn D, and benzyl alcohol, as well as standard assessments of maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}), and exposure (area under the concentration-time curve from time 0 to 12 hours (AUC_{0-12h})).

Summary of Results:

<u>Pharmacokinetic Study</u>

The PK study originally included 28 subjects who were assigned to NATROBA. Study center 104 enrolled eight subjects and all data from those subjects were removed for the PK analyses. As such, 20 subjects received open-label NATROBA and were included in the PK population. Of those subjects, 19 (95.5%) completed the study and 1 (5.0%) discontinued early. The subject who discontinued early did so for “other” reasons.

In the PK population, the subjects had a mean age of 9.6 years (range: 5 to 16 years). The majority of subjects were male (60.0%), most subjects were Hispanic or Latino (90.0%), and most were white (75.0%).

No subject in the PK population had measurable concentrations of spinosyn A or spinosyn D at any time up to 12 hours post application. As such, no concentration data or PK parameters were available for these metabolites.

Benzyl alcohol was quantifiable (above 1 µg/mL) in a total of nine plasma samples in six out of 19 subjects (32%): three out of ten subjects in the 5- to 9-year age group and three out of nine subjects in the 10- to 16- year age group (Table). The highest observed concentration was 3.94 µg/mL at 0.5 hours post-treatment but was below limit of quantification at 1-hour post-treatment for one subject in the 10 to 16 years age group. There were two subjects with a benzyl alcohol concentration at 3 hours post-treatment with the highest value of 3.53 µg/mL for one subject in the 5 to 9 years age group. Plasma concentrations were below limit of quantification (1 µg/mL) at 3.0-hour for all other subjects; no subject had measurable concentrations at the 6.0- and 12.0-hour time points. The mean (SD) C_{max}, T_{max}, and AUC_{0-12h} values for benzyl alcohol were 2.74 (1.11) µg/mL, 1.42 (1.24) hours, and 19.24 (-) µg•h/mL, respectively (Table).

The PK data indicated no systemic exposure for either spinosyn A or spinosyn D, and minimal systemic exposure for benzyl alcohol up to 12 hours postapplication among pediatric subjects who used a single topical, whole-body application of NATROBA. There were no unexpected safety signals or adverse safety trends observed during the study. Overall, NATROBA was generally safe and well tolerated in subjects 5 years of age and older after a single, whole-body application of study drug.

Table 24. Summary of Subjects with Measurable Benzyl Alcohol Concentrations

Subject ID	Time (h)	Conc (µg/mL)	Age (years)
101-PK (b) (6)	3	1.16	6
101-PK	0.5	1.45	5
	1	1.55	
	3	3.53	
101-PK	0.5	1.67	6
103-PK	0.5	3.94	16
103-PK	0.5	3.39	14
105-PK	0.5	2.1	16
	1	2.73	

Source: Reviewer's summary table based on Section 16.2.5 Compliance and/or Drug Concentration Data select Listing 16.2.10.1.

Table 25. Summary of Pharmacokinetic Parameters for Benzyl Alcohol (Study 303, PK Population)

Parameter Statistics	Natroba
C_{max} (µg/mL)	
n	6
Mean (SD)	2.737 (1.107)
Median	3.060
Minimum, Maximum	1.16, 3.94
CV%	40.453
Geometric Mean (Geometric SE)	2.509 (0.497)
T_{max} (hours)	
n	6
Mean (SD)	1.42 (1.242)
Median	0.75
Minimum, Maximum	0.5, 3.0
CV%	87.65
Geometric Mean (Geometric SE)	1.02 (0.365)
AUC_{0-12h} (µg•h/mL)	
n	1
Mean (SD)	19.240 (–)
Median	19.240
Minimum, Maximum	19.24, 19.24
CV%	–
Geometric Mean (Geometric SE)	19.240 (0.000)

Source: Table 2. Module 2.7.2 Summary of Clinical Pharmacology Studies
For a given subject, AUC_{0-12h} was not calculated if more than 3 plasma concentrations over a dosing interval for that subject were below the lower limit of quantification for benzyl alcohol (1.0 µg/mL); otherwise, plasma concentrations below the limit of quantification were set equal to the lower limit of quantification to provide an estimate of AUC_{0-12h}.
Abbreviations: AUC_{0-12h}, area under the concentration-time curve from time 0 to 12 hours; C_{max}, maximum observed plasma drug concentration; CV, coefficient of variation; PK, pharmacokinetics; SD, standard deviation; SE, standard error; T_{max}, time to maximum observed concentration

Reviewer comments:

1.) *Systemic exposure to benzyl alcohol at concentration of ~109.2 µg/mL (1.01 mmol/L) has been associated with neonatal gasping syndrome (Gershanik et al. 1982). The highest plasma benzyl alcohol observed in this the current study was 2.74 µg/mL or about 40-fold lower.*

2.) *In the current submission, using the same formulation currently approved for the treatment of head lice, the Applicant intends to establish the safety and effectiveness of NATROBA in the treatment of scabies infestations. NATROBA (spinosad) topical suspension, 0.9% is intended to be administered as a single treatment. According to the MUsT results (PK bioavailability study under maximal usage conditions) in 19 pediatrics subjects 5 to 16 years of age, the systemic exposure for spinosyn A and spinosyn D was not quantifiable, and limited systemic exposure for benzyl alcohol up to 12-hours post-treatment, which demonstrates similar bioavailability as what was observed in the studies in the original NDA submission.*

14.4.3. Bioanalytical Methods:

Benzyl Alcohol:

Benzyl alcohol concentrations in human heparinized plasma was evaluated using high-performance liquid chromatography (HPLC) with ultraviolet detection at 257 nm. The calibration range was 1.00 to 100 µg/mL. The method was adequately validated with precision and accuracy within acceptable limits with lower limit of quantification (LLOQ) at 1 µg/mL. Analysis was done by (b) (4).

Benzyl alcohol long term storage stability was demonstrated for 31 days at -20 ºC and -70 ºC. The samples were stored at -20°C until analysis. The long-term storage stability for benzyl alcohol is adequate.

Spinosyn A and Spinosyn D:

Spinosyn A and spinosyn D in human heparinized plasma was evaluated using HPLC-MS/MS assay. The calibration range was 3.00 to 1000 ng/mL for both spinosyn A and spinosyn D. The method was adequately validated with precision and accuracy within acceptable limits with LLOQ at 3 ng/mL.

Spinosyn A and spinosyn D in human plasma long term storage stability was demonstrated for at least 2076 days at -80 ºC. The samples were stored at -80 ºC until analysis. The long-term storage stability for spinosyn A and spinosyn D is adequate. Per the Bioanalytical Sample Analysis Workplan, PRO.0456-16270, the incurred sample reanalysis requirement was waived for both analytes because none of the samples showed quantifiable amounts of either analyte.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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