Spinosad at 0.9% in the treatment of scabies: Efficacy results from 2 multicenter, randomized, double-blind, vehicle-controlled studies

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Background: Scabies is a contagious skin disease resulting from *Sarcoptes scabiei* infestation. There are no approved over-the-counter treatments, and approved prescription products have disadvantages, including potential resistance. Spinosad, an insecticide derived from fermentation of a soil actinobacterium, shows promise as a potential treatment agent.

Objective: Combined results from 2 controlled clinical studies were used to evaluate the efficacy of 0.9% spinosad topical suspension in the eradication of scabies.

Methods: Each study included index subjects (the youngest household members with active scabies) and up to 5 other members in each household. Subjects applied 0.9% spinosad or vehicle once. Primary efficacy was the percentage of index subjects with complete cure on day 28. Additional efficacy included clinical cure, microscopic cure, and lesion counts.

Results: Spinosad at 0.9% is not equivalent to vehicle in the percentage of index subjects achieving complete cure on day 28 (78.1% vs 39.6%, respectively; $P < .0001$; n = 206). Additional efficacy analyses confirmed the consistent treatment effect of 0.9% spinosad. No safety signals were observed.

Limitations: The studies used small sample sizes to assess equivalency.

Conclusions: Spinosad at 0.9% performed better than vehicle in the treatment of scabies in these studies of subjects of 4 years of age or older following 1 application of study drug. (J Am Acad Dermatol 2022;86:97-103.)

Key words: efficacy; Natroba; pediatric; scabies; spinosad; topical.

INTRODUCTION

Scabies is a markedly pruritic, contagious skin infestation caused by the human itch mite, *Sarcoptes scabiei*.[1] Mites are small 8-legged parasites that burrow into the skin, inciting intense pruritus, which tends to worsen at night. The mites that infest humans are female, 0.3-0.4 mm in length, usually live 30-60 days, and can be seen with a magnifying glass or microscope.[2,3] Although they can crawl, scabies mites are unable to fly or jump.[1] The transmission of mites involves skin-to-skin contact between hosts, resulting in infestations between close

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contacts, such as friends and relatives. Sexual contact is also a common form of transmission.[1]

Although multiple drug products have been used to treat scabies, no single product has emerged with a strong risk-benefit profile.[4,5] Given the prevalence of scabies in the overall population (~300 million cases worldwide are reported annually[1]) and in light of emerging permethrin resistance,[6,7] the availability of a safe, well-tolerated, effective, single application treatment is critical.

CAPSULE SUMMARY

- Spinosad at 0.9%, as a targeted topical therapy, represents a new scabies treatment option for physicians and patients who otherwise have few choices.
- Spinosad at 0.9% has the potential to be an effective treatment for scabies due to its ability to reach mites in the stratum corneum, where they feed and reproduce.

Spinosad belongs to a chemical class of insecticides derived from the fermentation process of a naturally occurring soil actinobacterium, *Saccharopolyspora spinosa*.[8,9] Preclinical studies have shown that the active pharmaceutical ingredient, spinosad, is poorly absorbed through skin, is nonirritating to the skin of rabbits, is not a skin sensitizer, has no known skin toxicity, and is nongenotoxic (data on file, ParaPRO, LLC).[10]

A topical suspension containing 0.9% spinosad has been developed. This product was approved by the United States Food and Drug Administration in January 2011 (Natroba; ParaPRO, LLC) for the topical treatment of head lice infestations. Spinosad acts through a unique insecticidal mechanism. Specifically, spinosad is associated with the excitation of the nervous system in insects and alters the function of nicotinic and gamma-aminobutyric acid-gated ion channels.[11,12] This mechanism of action, spinosad's well-established safety and efficacy profile in the treatment of head lice, and the absence of reported resistance in lice and mites suggest the potential for spinosad to be used as a targeted topical therapy for the eradication of scabies.

To evaluate 0.9% spinosad in the treatment of scabies, 2 controlled, phase 3 clinical studies were conducted. In these studies, subjects with active infestations were treated with either active study drug or vehicle, along with all members of their households. The efficacy results of the 2 studies were pooled for analysis, and the combined results are presented herein.

METHODS

Study design and subjects

Both clinical efficacy studies were multicenter, randomized, double-blind, 2-arm, vehicle-controlled, 28-day evaluations of a single application of 0.9% spinosad. The efficacy variables, timing of efficacy assessments, and analysis methods were identical in the 2 studies. Prior to participating, all subjects (or their legal guardians) provided written informed consent and, if applicable, documented their assent. Institutional review board approvals of the protocols and consent or assent documents were obtained on March 10, 2017 for both studies. The studies were conducted between June 2017 and July 2018 across 13 study centers in the United States.

Each of the studies included index subjects (the youngest member in a household [4 years of age or older]) who had an active scabies infestation and up to 5 additional members of their household (regardless of infestation status). Confirmation of scabies was done by screening through reviews of clinical signs and symptoms (evidence of burrows or the presence of scabies inflammatory or noninflammatory lesions and pruritus), as well as through microscopic examinations of skin scrapings or dermoscopy to demonstrate the presence of mites, eggs, and/or scybala.

Approximately 120 index subjects were planned for randomization in each study. All members of each household must have agreed to participate in the study; thus, if any household member refused to provide consent or assent, none of the household members were enrolled. Further, all household members, regardless of infestation status, applied the same randomized, blinded study drug. Each of the studies assumed the average household would consist of 3 members, resulting in an enrollment of approximately 360 subjects (index and nonindex combined).

Designated personnel at each study center sequentially randomized eligible subjects in a 1:1 ratio (stratified by study center via a computer-generated schedule provided by the sponsor) to apply a single, blinded (subject and evaluator), topical dose of either 0.9% spinosad or vehicle. For a prespecified period prior to entry and throughout the study, all the subjects were prohibited from using scabies therapies other than the study drug.

Study drug application and clinical assessments

Randomized subjects were dispensed study drug on day 1, which was to be applied later at home on the same day as a single application over the entire body from the neck to the toes (including the soles of

Abbreviations used:

AE: adverse event

the feet) and to the scalp (if balding) or hairline, temples, and forehead. A caregiver assisted subjects younger than 12 years of age with study drug application. All subjects were instructed to rub the study drug into the skin, followed by a 10-minute waiting period before dressing. Subjects were further told not to shower or bathe for at least 6 hours after applying study drug.

A study visit was conducted on day 2 to confirm treatment compliance and perform safety evaluations. A brief follow-up visit was conducted by telephone on day 14 to assess adverse events (AEs). A final assessment visit was then conducted on day 28.

All subjects underwent skin examinations on days 1 and 28 to establish positive or negative evidence of active scabies infestation. The examinations were performed by investigators with experience and training relevant to the diagnosis and treatment of scabies. The examiners also received study-specific training at an investigator's meeting. The scabies assessments conducted on day 28 were used to determine whether the subject had achieved a clinical cure (defined as having all signs and symptoms completely resolved, including burrows, inflammatory or noninflammatory lesions, and pruritus) or a microscopic cure (defined as the microscopic or dermoscopic demonstration of the absence of mites, eggs, and/or scybala and negative dermoscopy result for burrows), or both.

The subjects' lesions were counted and, ultimately, were assessed to determine whether they had achieved a complete cure (defined as having both a clinical cure and a microscopic cure). Any infested subject who failed to achieve complete cure on day 28 was provided with 5% permethrin and directed to their primary care physician for follow-up.

Statistical methodology

The efficacy analysis was conducted using the index intent-to-treat population, which included all index subjects who were randomized to study drug. Safety was assessed using all subjects (index and nonindex) who applied study drug.

In both studies, the primary efficacy endpoint was the percentage of index subjects who achieved complete cure on day 28. The difference in percentages between study drug groups was tabulated, along with 2-sided 95% CIs. A Cochran-Mantel-Haenszel general association test adjusted by study center stratification (low enrolling study centers were pooled) was performed to test for equivalence at an α level of 0.05. In the analysis, subjects with missing data on day 28 were counted as failures if they discontinued the study due to lack of efficacy or an AE related to study drug. All other subjects with missing data on day 28 had their outcomes imputed using the last observation carried forward method.

The sample size was based on the results of a proof-of-concept evaluation and published literature that were suggestive of a 30% delta between study drug groups for the primary endpoint. Based on a Fisher's exact test, 48 index subjects per study drug group would provide 80% power to declare 0.9% spinosad was not equivalent to vehicle in each of the studies. The sample size was increased slightly to allow for dropouts.

Additional efficacy endpoints evaluated on day 28 consisted of the following: percentage of subjects achieving clinical cure; percentage of subjects achieving microscopic cure; number of new lesions present and changes from baseline in total lesions based on mapping from baseline assessments; and percentage of all randomized subjects (index and nonindex) who were infested at baseline and subsequently achieved a complete cure.

With the exception of lesion counts, the additional efficacy endpoints were analyzed using the same methods as the primary endpoint. The difference between study drug groups for the number of new lesions was determined using a negative binomial regression model. The change from baseline in total lesions was evaluated using an analysis of covariance. Both these analyses included study drug group and study center as fixed factors and baseline total lesion count as a covariate.

RESULTS

Subject demographics and disposition

Overall, 551 subjects (index and nonindex) were randomized and evaluated for efficacy (n = 296 of 0.9% spinosad; n = 255 vehicle). Most subjects (96.2%) completed the studies. Of those who discontinued early, most (15 of 21 [71.4%]) were lost to follow-up. No subject discontinued due to an AE.

The index subjects (n = 105 of 0.9% spinosad; n = 101 vehicle) had a mean age of 39.28 years (range, 4-80 years) (Table I). Most were women (57.3%), White (77.7%), and Hispanic or Latino (55.8%). All 206 index subjects had an active scabies infestation at baseline, and approximately one-third (32.5%) had a history of prior scabies infestations. Of the index subjects at baseline, all had evidence of

Table I. Summary of subject demographics and baseline characteristics for index subjects

Demographic characteristics	Vehicle n (%) (N = 101)	Spinosad n (%) (N = 105)	Total n (%) (N = 206)
Age (y)			
Mean (SD)	39.32 (19.40)	39.25 (19.13)	39.28 (19.22)
Median	43.0	39.0	41.0
Min, max	5, 80	4, 76	4, 80
Sex (n, %)			
Male	42 (41.6)	46 (43.8)	88 (42.7)
Female	59 (58.4)	59 (56.2)	118 (57.3)
Ethnicity (n, %)			
Hispanic or Latino	58 (57.4)	57 (54.3)	115 (55.8)
Not Hispanic or Latino	43 (42.6)	48 (45.7)	91 (44.2)
Race (n, %)			
Asian	4 (4.0)	4 (3.8)	8 (3.9)
Black or African American	14 (13.9)	19 (18.1)	33 (16.0)
Native Hawaiian or Other Pacific Islander	2 (2.0)	0	2 (1.0)
White	79 (78.2)	81 (77.1)	160 (77.7)
Other	2 (2.0)	1 (1.0)	3 (1.5)
Evidence of burrows (n, %)			
Yes	80 (79.2)	81 (77.1)	161 (78.2)
No	21 (20.8)	24 (22.9)	45 (21.8)
Evidence of lesions (n, %)			
Yes	101 (100)	105 (100)	206 (100)
No	0	0	0
Evidence of pruritus (n, %)			
Yes	100 (99.0)	105 (100)	205 (99.5)
No	1 (1.0)	0	1 (0.5)
Total number of pre-existing lesions			
Mean (SD)	14.77 (12.87)	15.63 (14.03)	15.21 (13.45)
Median	12.0	12.0	12.0
Min, max	1, 100	1, 100	1, 100
Score of lesions (n, %)*			
Free of lesions	0	0	0
Mild	40 (39.6)	44 (41.9)	84 (40.8)
Moderate	59 (58.4)	59 (56.2)	118 (57.3)
Severe	2 (2.0)	2 (1.9)	4 (1.9)
Microscopy or dermoscopy result (n, %)			
Negative	0	0	0
Positive	101 (100)	105 (100)	206 (100)
Active scabies infestation (n, %)			
Yes	101 (100)	105 (100)	206 (100)
No	0	0	0
Prior scabies infestation (n, %)			
Yes	36 (35.6)	31 (29.5)	67 (32.5)
No	65 (64.4)	74 (70.5)	139 (67.5)

Numbers are based on the index intent-to-treat population. All subjects are summarized based on their assigned, randomized study drug group; no subject had a drug misallocation.
max, Maximum; *min*, minimum.
*Mild, ≤10 lesions; moderate, 11-49 lesions; severe, ≥50 lesions.

lesions and all had a positive microscopy or dermoscopy result; in particular, most had evidence of burrows (78.2%) and pruritus (99.5%). The mean number of pre-existing lesions at baseline among index subjects was 15.21, and of those with lesions, most (57.3%) had 11-49 lesions (equating to moderate).

Efficacy results

The combined study results demonstrated that 0.9% spinosad is not equivalent to vehicle in the rate of complete cure of scabies. On day 28, a greater percentage of index subjects exhibited complete cure in the 0.9% spinosad group compared with those in the vehicle group (78.1% vs 39.6%,

respectively). The difference (95% CI) between the groups was significant (38.4% [26.3% is Natroba and 50.5% is vehicle]; $P < .0001$) (Table II).

Sensitivity analyses based on evaluations that did not impute missing data (ie, used observed data) or that used only multiple imputation or last observation carried forward methods demonstrated the robustness of the result. An analysis using an index per protocol population (a subset of the index intent-to-treat population that excluded index subjects with protocol deviations that could have confounded the analysis) further confirmed the strong efficacy results. In all sensitivity analyses, a positive treatment effect favoring 0.9% spinosad over vehicle was observed ($P < .001$ for each pairwise comparison [data not shown]).

Regarding the additional endpoints on day 28, 0.9% spinosad showed greater efficacy relative to vehicle based on the percentages of index subjects with clinical and microscopic cures ($P < .001$ for pairwise comparisons in each endpoint) (Table III). Index subjects in the 0.9% spinosad group relative to the vehicle group were also less likely to develop new lesions ($P < .001$); spinosad at 0.9% was favored over vehicle in the mean change from baseline in total lesion counts ($P = .001$). Finally, a greater percentage of all randomized subjects who were infested at baseline in the 0.9% spinosad group relative to the vehicle group achieved a complete cure ($P < .001$).

Key safety findings

For the combined studies, none of the individual events experienced by subjects in the 0.9% spinosad group (n = 306) occurred in ≥1% of the subjects. The only individual events experienced by more than 1 subject each were abdominal pain, back pain, burning sensation, cough, headache, neck pain, and decreased weight, each of which occurred in 2 subjects (0.8%) (data not shown). The only events considered by the investigator to be related to 0.9% spinosad consisted of burning sensation (2 subjects [0.7%]) and dry skin (1 subject [0.3%]); both events occurred shortly after study drug application.

DISCUSSION

Approved, topical prescription therapies for the treatment of scabies principally include products containing permethrin, lindane, and crotamiton. Other prescription therapies, including topical malathion and both oral and topical ivermectin, are sometimes used off label. Each of these products has substantial disadvantages, such as the limited availability of efficacy data (in the case of off-label uses) and risks that variously include resistance, exacerbation of skin irritation, and contraindications in children and pregnant women. There are no approved over-the-counter treatments for scabies, although sulfur-containing soaps and creams, along with 1% permethrin (Nix; Prestige Consumer Healthcare Inc), which is indicated for the treatment of head lice, have been used. Sulfur, at concentrations necessary to treat scabies, is not readily available, and its efficacy has not been rigorously established. Permethrin is effective at killing both mites and eggs, but at a concentration of 5%, not the 1% found in Nix.[13] Critically, resistance to permethrin-based and ivermectin-based products has been documented since at least 2000 in the clinical setting.[5,14,15]

Spinosad at 0.9%, as a targeted topical therapy, represents a pharmacologic advancement for the treatment of scabies. Spinosad at 0.9%, which has not previously been evaluated in scabies, has no known evidence of emerging resistance. The efficacy of 0.9% spinosad, as shown by nonclinical studies (data on file), is derived from the active ingredient's ability to reach mites where they feed and reproduce (ie, in the stratum corneum), while never penetrating deeper before sloughing off through desquamation. Thus, 0.9% spinosad represents a new treatment option for physicians and patients who otherwise have few approved choices.

The combined results of the clinical studies presented herein show the treatment effect of 0.9% spinosad in the eradication of scabies and, specifically, demonstrate that 0.9% spinosad is not equivalent to vehicle in regard to achieving complete cure 28 days after a single application. The additional efficacy assessments further confirmed the ability of 0.9% spinosad to eradicate scabies in terms of both observed reductions in related signs or symptoms and microscopically determined eradication of mites. Based on AE reporting, 0.9% spinosad appeared to be well tolerated and did not raise safety concerns. Of note, in April 2021, based largely on these results, the United States Food and Drug Administration approved 0.9% spinosad for the treatment of scabies infestation in patients 4 years of age and older.

By including household members, regardless of whether they had active infestations, the studies controlled for the potential of cross-infestation and reinfestation. The population of subjects was evaluated, and the methods employed in their evaluations, which included assessments consistent with those typically used in clinical practice, allowed the studies to mimic a real-world treatment environment. Because male mites typically live on the skin's

Table II. Summary of index subjects who exhibited complete cure of scabies on day 28 (primary efficacy endpoint)*

Complete cure on Day 28	Vehicle n (%) (N = 101)	Spinosad n (%) (N = 105)
Yes, n (%)	40 (39.6)	82 (78.1)
No, n (%)	61 (60.4)	23 (21.9)
Proportion difference		38.4
95% CI for difference		26.3-50.5
P value		<.0001

I-ITT, Index intent-to-treat.
*The I-ITT population included only index subjects who were randomized to receive the study drug. All subjects were assessed for efficacy based on their assigned, randomized study drug group; no subject had a drug misallocation. Differences represent spinosad − vehicle. The primary imputation method was used to impute missing data. The *P* value for testing the difference in proportions between spinosad and vehicle was based on a Cochran-Mantel-Haenszel general association test adjusted by study center.

Table III. Summary of additional efficacy results for index subjects

Additional efficacy results	Vehicle (N = 101) n (%)	Spinosad (N = 105) n (%)
Clinical cure on day 28 (I-ITT population)*		
Yes, n (%)	40 (41.2)	82 (79.6)
No, n (%)	57 (58.8)	21 (20.4)
Proportion difference		38.4
P value		<.001
Microscopic cure on day 28 (I-ITT population)*		
Yes, n (%)	51 (52.6)	85 (85.9)
No, n (%)	46 (47.4)	14 (14.1)
Proportion difference		33.3
P value		<.001
New lesions (I-ITT population)†		
Number of events	162	125
Estimate of rate (95% CI)	0.05 (0.03, 0.09)	0.01 (0.00, 0.01)
Estimate of rate ratio (95% CI)		0.11 (0.04, 0.35)
P value		<.001
Total lesion counts (I-ITT population)‡		
Baseline, mean (SD)	14.8 (12.87)	15.6 (14.03)
Day 28, mean (SD)	8.7 (12.01)	4.1 (15.98)
Change from Baseline, mean (SD)	−6.2 (11.05)	−11.4 (12.35)
Change from Baseline, LSM (SE)	−6.9 (1.11)	−11.9 (1.09)
Difference in LSM (SE)		−5.0 (1.50)
P value		.001
Complete cure on day 28 in subjects infested at baseline (ITT population)*,§		
N	137	155
Yes, n (%)	49 (37.4)	111 (78.2)
No, n (%)	82 (62.6)	31 (21.8)
Proportion difference		40.8
P value		<.001

The I-ITT population included only index subjects who were randomized to the study drug. The ITT population included all subjects (index and nonindex combined) who were randomized to the study drug. All subjects were assessed for efficacy based on their assigned, randomized study drug group; no subject had a drug misallocation.
I-ITT, Index intent-to-treat; *ITT*, intent-to-treat; *LSM*, least squares mean.
*Difference represents spinosad − vehicle. The primary imputation method was used to impute missing data. The *P* value for testing the difference in proportions between spinosad and vehicle was based on a Cochran-Mantel-Haenszel general association test adjusted by study center.
†The last observation carried forward method was used to impute missing data. The *P* value represents testing the difference in event rates (ie, new lesions) between spinosad and vehicle from a negative binomial regression analysis.
‡The *P* value was based on an analysis of covariance with study drug group and study center (low enrolling study centers were pooled) as factors and the baseline total lesion counts as covariates.
§The primary imputation method was used to impute missing data.

surface, manually rubbing and scratching may reduce infestation and partially account for the efficacy observed in the vehicle group. Nevertheless, the magnitude of the difference between active and vehicle groups (38.4%) was both statistically significant and clinically meaningful. Although the sample size was limited, the results are nevertheless readily applicable to (ie, can be readily extrapolated to) a general population of patients seeking treatment for scabies.

CONCLUSIONS

Spinosad at 0.9% performed better than vehicle in the eradication of scabies when applied as a single topical treatment from the neck down and left on the skin for a least 6 hours prior to being washed off. Limited safety findings suggest that the product is well tolerated by subjects as young as 4 years of age.

Anthony J. Mancini, MD, Head of Dermatology at Ann & Robert Lurie Children's Hospital of Chicago and Professor of Pediatrics and Dermatology, Northwestern University Feinberg School of Medicine, was a nonauthor contributor who provided editorial review and assistance. Medical writing support was provided by Illuminated Research, LLC.

Conflicts of interest

Drs Seiler and Keech were investigators on the studies. Ms Aker and Drs Miller and Belcher served as paid consultants contributing to the study design and conduct. Mr Mettert is an employee of ParaPRO LLC.

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