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Evaluating Clinical Study Results of a New Nonsteroidal Topical Treatment for the Management of Seborrheic Dermatitis

Guest Editor: James Q. Del Rosso, DO
Dermatologist
Las Vegas Skin and Cancer Clinics
Las Vegas, NV

FACULTY
Boni E. Elewski, MD
Vice-Chair for Clinical Affairs
Professor of Dermatology
University of Alabama at Birmingham
Department of Dermatology
Birmingham, AL

Leon H. Kircik, MD, FAAD
Associate Clinical Professor of Dermatology
Indiana University Medical Center
Medical Director
Derm Research, PLLC
Louisville, KY

Mr Vijendra Nalamothu
Senior Director, Research & Development
Promius Pharma, LLC
Bridgewater, NJ

Ann L. O’Leary, PhD
Senior Manager
Ricerca Biosciences, LLC
Concord, OH

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Concord, OH


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Evaluation of a nonsteroidal topical cream in a guinea pig model of *Malassezia furfur* infection

Vijendra Nalamothu\textsuperscript{a,⁎,☆}, Ann L. O'Leary, PhD\textsuperscript{b}, Sateesh Kandavilli, PhD\textsuperscript{a}, Joanne Fraser, PhD\textsuperscript{a}, Vishvabhavan Pandya, MD\textsuperscript{a}

\textsuperscript{a}Research and Development, Promius Pharma, LLC, Bridgewater, NJ 08807, USA

\textsuperscript{b}Ricerca Biosciences, LLC, Concord, OH 44077, USA

**Abstract** *Malassezia furfur* is an important causal factor for seborrheic dermatitis, and topical antifungal therapy is an effective treatment approach. This study assessed the antifungal activity of Promiseb Topical Cream (Promius Pharma, LLC, Bridgewater, NJ), a novel nonsteroidal prescription medical device cream, in the *M furfur*-infected skin model for guinea pigs. Guinea pigs (N = 28) were divided into 4 groups and infected with *M furfur* for 7 days. On day 8, the first group of animals was sacrificed. The scrapings of inoculation site on each animal were tested for the presence of the organism, and the skin was excised for quantitation of *M furfur*. The second group was left untreated. The remaining 2 groups were treated with one of the test agents (Promiseb) and the positive control product (ciclopirox olamine cream, 0.77%; Loprox, Medicis, Scottsdale, AZ) each once daily for 3 days. At the end of treatment, animals were sacrificed and analyzed similarly to the first group. *M furfur* was recovered from all animals in the first group. Visual signs of infection, such as erythema and edema, were not observed in the infected animals at the end of the study. In the animals treated for 3 days with the test agents, the *M furfur* counts were reduced to below the limit of quantitation. Both test agents were equally effective in substantially reducing the density of *M furfur* compared with the untreated control.

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**Introduction**

Although the etiology of seborrheic dermatitis has not been fully elucidated, there is strong evidence that the disease is caused by several different factors, including increased sebaceous activity, immunologic and inflammatory abnormalities, neurologic involvement, and the presence of a variety of fungi, including *Malassezia furfur*. Recent research has focused on a probable constellation of causative factors, such as increased sebum activity and the presence of *Malassezia* yeasts.

*M furfur* is found among normal human skin microflora, but yeasts of the genera predominate on sebum-rich areas of the skin, such as the trunk, face, scalp, ears, forehead, nasolabial folds, labella, and beard area.\textsuperscript{1} The purported causal relationship of *M furfur* to seborrheic dermatitis pathogenesis is implied because this yeast can be isolated in patients with seborrheic dermatitis and because the disease
responds to antifungal agents. The Malassezia species of yeast and its involvement and combination of both nonspecific and specific nonimmune and immune mechanisms in seborrheic dermatitis is controversial because it is uncertain which mechanisms will dominate and it is dependent on microorganism activity and yeast virulence and number.

The current study evaluated the antifungal activity of Promiseb Topical Cream (Promius Pharma, LLC, Bridgewater, NJ), a novel nonsteroidal prescription medical device cream cleared by the US Food and Drug Administration (FDA) in an M furfur-infected skin model in guinea pigs.

Materials and methods

The animals in this study were cared for in compliance with acceptable research standards for animal experimentation.

Animals and animal care

The study used male Hartley albino guinea pigs (Hilltop Lab Animals, Inc, Scottsdale, PA) that weighed approximately 400 g. Food and water were available ad libitum. All animals were acclimatized to the laboratory conditions for 2 days before the beginning of dosing.

Test materials

The test material was Promiseb Topical Cream, a novel nonsteroidal prescription medical device cream (Promius Pharma, LLC, Bridgewater, NJ), and the positive control product was ciclopirox olamine cream, 0.77% (Loprox, Medicis, Scottsdale, AZ). Both were supplied by Promius Pharma and were stored at controlled room temperature.

Test microorganism and control and test compound

The test microorganism, M furfur (ATCC 14521), was grown on Sabouraud dextrose agar and 1% olive oil. Colonies were transferred to Dixon’s broth and grown with shaking at 35°C for 4 to 7 days. On each day of infection, an aliquot of the suspension was removed and centrifuged, and the pellet was resuspended in sterile phosphate-buffered saline. The concentration of the suspension was adjusted with the aid of a spectrophotometer to approximate 10^7 colony-forming units (CFU)/mL. The actual concentrations were determined using the dilution plate count method and contained 1.04 × 10^7 to 2.08 × 10^7 CFU/mL.

Study design

The animal model for the skin infection of M furfur was adopted, with minor modifications, from previous reports.

Table 1 describes the treatment groups used in this experiment. The dorsal hair was removed from each animal with electric clippers, and 0.2 mL of the suspension of M furfur was applied to a 3- to 4-cm² area on the dorsal skin of each animal and gently rubbed in with a cotton swab. The animals were infected in this manner each day for 7 consecutive days.

One day after the last infection, the dorsal hair was removed again from each animal with electric clippers. The four animals in the first group were sacrificed. The inoculation site on each animal was scraped with the blunt side of a sterile scalpel blade, and the blade was rinsed into a tube of Dixon’s broth to determine the presence of organism. The inoculated skin was excised for quantitation of M furfur (as described subsequently), and the first treatment was then applied to animals in groups 3 and 4. A 0.5-g aliquot of each of the test materials was gently rubbed into the inoculated area of each animal. This process was repeated on the next 2 consecutive days for a total of three treatments. No treatments were applied to the infected control animals in the second group. Animals were observed daily for any adverse signs.

One day after the last treatment, the dorsal hair was removed from all animals with electric clippers. The animals were then sacrificed, the inoculation sites were sampled, and the skin was excised as described.

Processing skin samples for the quantification M Furfur

The skin scrapings were placed into tubes of Dixon’s broth and incubated with shaking at 35°C for 48 hours. A 10-mL sample was removed from each tube with an inoculating loop, spread onto a modified Leeming-Notman plate, and incubated at 35°C for 48 hours. The plates were then evaluated for growth of M furfur.

Each skin sample was placed in a tared, sterile tube, each tube was weighed, and the weight of the sample was determined. An aliquot (5 mL) of sterile phosphate-buffered saline was added to each tube, and the contents were macerated with a tissue homogenizer (Polytron PT 3100, Kinematica AG, Littau, Switzerland). Aliquots of the homogenate were sequentially diluted and plated on modified Leeming-Notman agar and incubated at 35°C for
3 days. Colony counts were used to determine the number of CFUs/g of skin tissue.

Results

*M. furfur* was recovered from the skin scrapings and skin samples taken from all four animals of the first group (infection control). The results are given in Table 2. No visual signs of infection, such as erythema or edema, were observed on any of the animals after 7 days of infection. The severity of infection was observed to be less than reported in another study.6 The mean density of *M. furfur* in the skin samples on day 7, before initiating the treatment with the test substances, was observed to be log$_{10}$ 5.03 CFU/g of skin tissue.

The skin scrapings collected from all of the infected control animals 1 day after the final treatment were each positive for *M. furfur*. The mean density of the organism recovered from the skin samples was log$_{10}$ 3.61 CFU/g of tissue. The organism was not detected in the skin scrapings from the animals treated with the nonsteroidal cream or the ciclopirox olamine cream. Furthermore, the organism was not recovered from the homogenized skin samples. Both of these treatments were effective in substantially reducing the density of *M. furfur* compared with the infected control.

Discussion

The results of this study confirm that the new nonsteroidal cream is effective in significantly reducing the population of *M. furfur* on the skin of guinea pigs compared with untreated controls. Although the exact mechanism remains to be proved, the pathogenic role of *M. furfur* in skin conditions such as seborrheic dermatitis and dandruff is becoming more obvious.3-5 Treatment studies have demonstrated that disease remission is associated with a reduction in the number of these organisms on the skin and that recolonization with the fungus leads to a recurrence of disease.11-14

Conclusions

The current study findings support that both test agents were equally effective in substantially reducing the density of *M. furfur* compared to untreated control and confirm the efficacy of the nonsteroidal cream for the treatment of seborrheic dermatitis, because *M. furfur* is a strong causative factor in its disease pathogenesis.

References

An open-label, single-center pilot study to determine the antifungal activity of a new nonsteroidal cream (Promiseb Topical Cream) after 7 days of use in healthy volunteers

Leon Kircik, MD, FAAD*

Department of Dermatology, Indiana University Medical Center, Bloomington, IN 47405-7000, USA

Abstract

Topical corticosteroids are effective for the treatment of seborrheic dermatitis. The duration of treatment with mid- to high-potency formulations is limited by the well-known side effects associated with their long-term use; further, topical corticosteroids treat only the inflammation associated with the disease. This study assessed the antifungal activity of a new corticosteroid-free cream against Malassezia spp, which may be an important pathogenic factor in seborrheic dermatitis. This was a single-center, bilateral, open-label pilot study in 10 healthy volunteers. The nonsteroidal cream was applied twice daily to a designated target area on the chest for 7 days, and the number of colony-forming units of Malassezia spp taken by tape stripping after 7 days was compared with baseline. The percentage reduction from baseline to day 7 in the number of colony-forming units of Malassezia spp was 94% on the treated side versus 49% on the untreated side (P = .03). This pilot study shows the nonsteroidal topical cream has antifungal activities. Further exploration into its potential as a therapeutic alternative for seborrheic dermatitis is warranted.

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Introduction

The pathogenesis of seborrheic dermatitis has not yet been fully described, but some combination of excessive sebum production, fungal activity, and inflammatory and immunologic factors is likely. Malassezia spp, which are a normal part of skin flora, have been implicated in disease pathogenesis. These yeasts depend on exogenous lipids for survival, and as a result, they tend to colonize areas of the skin that are rich with sebum.1,2

Although most would agree that Malassezia spp have an important effect in disease pathogenesis, how these organisms actually induce skin lesions has not been established. Numerous quantitative studies have failed to show significant differences between the numbers of yeast cells on patients with seborrheic dermatitis versus those on healthy controls, but one study has characterized different Malassezia spp for their specific pathogenicity.3

Other potential pathologic mechanisms that may trigger the response to Malassezia spp are underlying abnormal immune response, defective skin barrier function, and an...
inflammatory response arising from the body’s susceptibility to irritating free fatty acids released by these yeasts (Figure 1). Other potential disease factors that are being investigated with seborrheic dermatitis are hormonal fluctuations, perhaps in concert with sebum production, neurologic factors, and exogenous factors such as lack of sunlight and eating disorders.

Whatever the exact drug or device mechanisms are, the important clinical consideration is how pathogenesis dictates treatment. Even without a full understanding of how the disease develops, inflammatory and fungal components to the disease are evident, because it responds both to topical corticosteroids and to topical antifungal agents.

No gold standard treatment has been developed for seborrheic dermatitis, but most cases can be managed effectively with a topical corticosteroid, a keratolytic, a topical antifungal or sulfur product, or some combination of these agents. Topical corticosteroids are effective anti-inflammatory agents, but the long-term use of mid- to high-potency corticosteroids is associated with well-known effects such as skin atrophy, striae, and telangiectasia. Keratolytics are peeling agents that are very effective in reducing flaking and scaling and are useful for removing the dense scale associated with severe disease.

Antifungal agents are very useful for reducing the fungal component of seborrheic dermatitis. Malassezia spp likely exert proinflammatory reactions through alterations in lipase activity, which induces complement activation through alternative pathways, thus leading to inflammation. Therefore, it is intuitive that reduction of Malassezia spp in a patient with seborrheic dermatitis may also mitigate the inflammatory reaction to these yeasts.

Promiseb Topical Cream (Promius Pharma, LLC, Bridgewater, NJ), a nonsteroidal prescription medical device cream evaluated in this study, is a new prescription agent indicated for the treatment of seborrheic dermatitis. A previous study demonstrated that the nonsteroidal cream is an effective and well-tolerated agent for the treatment of mild to moderate seborrheic dermatitis of the face. This contribution reports the results of an open-label pilot study in healthy volunteers that assessed the antifungal activity of this new nonsteroidal cream after 7 days of use.

Methods

Study objective

The primary objective of this study (Protocol number PSC0802, Ph IV) was to determine if 7 days of twice-daily treatment with nonsteroidal cream had any clinical antifungal activity, specifically against Malassezia spp, which are considered causative organisms in seborrheic dermatitis.

Study participants

Enrollment was planned for no more than 10 participants. Eligible persons had to be at least 18 years old and have healthy skin areas on the chest that were free of excessive hair. Women of childbearing potential had to have a negative urine pregnancy test at baseline and practice a reliable method of contraception throughout the study.

Individuals with dandruff were ineligible for inclusion, if they were unwilling to stop treatment for dandruff during the study. The study excluded individuals who had treated their chest with any topical antiseborrheic dermatitis or antidandruff product, had used systemic antifungals or systemic medication that could interfere with the study or place them at undue risk, or had participated in the study of an investigational drug within 30 days before baseline.

Enrolled individuals were prohibited from using other topical medications or products (eg, moisturizers) on the chest, and treatment of the scalp with antidandruff shampoo during the study was prohibited. Only nonmedicated cleansers were permitted. Finally, the study excluded participants with chronic or active liver disease, renal impairment, or any other disease that would interfere with the study or place them at undue risk or who were in any way unable to comply with study requirements.

Study design and treatment

This was a single-center, bilateral, open-label study. Healthy volunteers applied Promiseb Topical Cream, a new nonsteroidal cream, twice daily to a designated target area on the chest for 7 days. These target areas, one on the left and one on the right, were identified and marked with semipermanent ink. The left side was designated the untreated side. A small amount of the test drug, approximately the size of a green pea, was applied twice daily every
12 hours to the treatment site on the right. The volunteers were instructed not to wash the treated area for at least 8 hours after application of test drug.

Sampling and cultures

At the baseline visit and on day 7, the investigator took a superficial skin sample using a 2- by 3-cm strip of clear tape from both the right and the left target areas. The tape was placed on an agar plate, and colonies were counted after 7 days of incubation. Sampling and culturing techniques were based on the previously published methods.7

Study variables

The number of colony-forming units of Malassezia spp on the tape strips was the primary study variable. Adverse events (AEs) were monitored at each visit. The incidence rate of treatment-emergent AEs was the primary safety parameter.

Treatment and protocol adherence

At visit 2, the investigator interviewed participants regarding treatment adherence and asked if any doses were missed or if the treatment regimen had been altered since the last visit. The investigator asked about adherence to study requirements, and all protocol deviations were recorded on the case report form.

Statistical considerations

The intent-to-treat population was the primary analysis data set, which consisted of all enrolled participants. Missing data were not imputed. Reduction and percent reduction from baseline in colony-forming units were calculated for each person for treated and untreated sites, and the percentage reduction was compared using the t test.

Results

Participant disposition

Ten individuals (80% men) were enrolled in this study, and ethnicity was split evenly between African American and Caucasian. Their mean age was 45 years (range, 24-61 years). All participants completed the study. Two protocol deviations were noted. Two participants used two extra doses of the study product (ie, the night before and the morning of the final visit).

Antifungal activity

Among the samples collected at the baseline visit, colonies were observed on the plates for seven of the 10 individuals (Table 1). The colonies resembled those of the standard M furfur strain. Of the seven participants with positive samples, three participants (Nos. 1, 3, and 9) had very low numbers of colonies (<5 colonies/cm²), whereas the remaining four had numerous colonies, ranging from 13 to 58 colonies/cm² in participant 7 to 138 to 195 colonies/cm² for participant 2 (Table 1). In general, the left-side samples yielded more colonies than did the right-side samples.

The densities of colonies from samples collected at the day 7 visit were generally lower than the densities from baseline samples. In all participants from whom organisms were recovered, the magnitude of the difference in samples was greater for the treated side than for the untreated side. Among those individuals with more than 5 colonies/cm², reductions on the untreated side ranged from 58% to 65% and reductions on the treated side ranged from 85% to 93%. The three participants (Nos. 4, 5, and 6) whose baseline samples yielded no growth were still negative at the day 7 visit.

From baseline to the day 7 visit, there was a mean reduction of 34.4 colonies/cm² (94% reduction) on the treated side and a mean reduction of 29.7 colonies/cm² (49% reduction) on the untreated side (Figure 2). The intergroup difference in percentage reduction of the number of colonies in each group was significantly different (P = .03) between the treated and the untreated sides of the body. These results suggest that the nonsteroidal topical cream is effective in reducing the number of colony-forming units of Malassezia spp on the treated site compared with the untreated control site.

![Table 1](Image)

<table>
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<th>Subject</th>
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S46 L. Kircik
Adverse events

All enrolled individuals were included in the safety analysis, and no serious AEs were documented. One individual reported an infected tooth, but this AE was deemed unrelated to the study medication.

Discussion

This study showed that the nonsteroidal cream is effective in reducing the number of colony-forming units of *Malassezia* spp in healthy volunteers, which was demonstrated by a significantly greater reduction in the number of colony-forming units of *Malassezia* spp than that achieved with no treatment.

Even with the small sample size, reduction in colony counts on the treated side was statistically significantly greater than on the untreated side. The 94% reduction in *Malassezia* density after 7 days of treatment seems likely to be clinically significant.

Seborreic dermatitis is a common skin disease that is characterized by significant variations in severity between individuals and over time in the disease history of each patient. These patterns underscore the importance of providing the patient with a varied armamentarium of drugs in different vehicles that can address different etiologies, severities, skin location, patient responses to therapy, and patient preference. This new nonsteroidal cream can be beneficial to the patient, because it does not pose the same long-term risks associated with corticosteroid use and can be applied on any body area, including sensitive, thin areas of the skin such as the face.

Importantly, the nonsteroidal cream having the ability to reduce the population of *Malassezia* spp, the cream also may mitigate the inflammatory response. There are fewer fungi to interact with free fatty acids, which likely is a pivotal mechanism of disease pathogenesis. The reduction of fungi, coupled with the resultant reduction of inflammation, is an important point for further investigation because this might suggest that the nonsteroidal cream could be ideal for long-term disease management.

Conclusions

These results suggest that the new nonsteroidal cream is a promising new nonsteroidal therapy for patients with seborrheic dermatitis, and further investigation into its efficacy and safety, as monotherapy or in combination with other therapies for patients with seborrheic dermatitis, is warranted.

References

5. Elewski B. An investigator-blind, randomized, 4-week, parallel-group, multicenter pilot study to compare the safety and efficacy of a nonsteroidal cream (Promiseb Topical Cream) and desonide cream 0.05% in the twice-daily treatment of mild to moderate seborrheic dermatitis of the face. Clin Dermatol 2009;27(Suppl 2):S48-53.
An investigator-blind, randomized, 4-week, parallel-group, multicenter pilot study to compare the safety and efficacy of a nonsteroidal cream (Promiseb Topical Cream) and desonide cream 0.05% in the twice-daily treatment of mild to moderate seborrheic dermatitis of the face

Boni Elewski, MD *

Department of Dermatology, University of Alabama at Birmingham School of Medicine, Ste 414, 700 18th St S, Birmingham, AL 35233-3805, USA

Abstract

The treatment of seborrheic dermatitis includes topical antifungal agents to eradicate Malassezia spp, corticosteroids, which treat the inflammatory component of the disease and keratolytics which remove scale and crust. This study compared the efficacy of a nonsteroidal topical cream and a low-potency topical corticosteroid for the treatment of mild to moderate seborrheic dermatitis of the face in 77 volunteers randomized to twice-daily treatment with nonsteroidal cream or corticosteroid cream for up to 28 days. If the individual was rated clear by day 14, the study drug was collected and the participant was told not to use any topical products on the previously treated areas until after the 28-day follow-up visit. Both treatments were similarly effective in reducing disease severity, with approximately 90% of participants clearing or almost clear during the study. Both treatments demonstrated significant reductions in erythema, scaling, and pruritus ($P < .0001$). Safety in both groups was rated as excellent in more than 90%. Those using the nonsteroidal cream who cleared after 14 days of treatment were more likely to remain clear than were participants using the corticosteroid cream ($P = .0173$). Investigator global assessments of improvement found both study agents were essentially the same, and participants in both groups achieved clinically important improvement.

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Introduction

The cycle of remission and flare that characterizes seborrheic dermatitis requires treatment to manage acute symptoms as well as to provide long-term prophylaxis to minimize the frequency and severity of recurrences. Although the pathogenesis of the disease is not fully understood, its etiology is multifactorial and includes...
increased sebum activity, *Malassezia* spp colonization, and individual susceptibility. Treatment should address at least two of these causes whenever possible; disease severity, anatomic location, and patient preference also should be considered when selecting a treatment.

The three primary treatment classes used for seborrheic dermatitis are keratolytics, topical corticosteroids, and antifungals, and these medications come in a variety of vehicles, including shampoo, cream, lotion, gel, and foam to help tailor therapy to the particular needs of the patient. Keratolytics remove the scale and crust of seborrheic dermatitis, which helps improve the appearance of the skin while maximizing the absorption of other topical treatments. Medicated shampoos should contain a keratolytic such as tar or an antifungal such as pyrithione zinc or selenium sulfide, and they can be used in severe disease to remove thick scale to improve penetration of a topical corticosteroid.

Topical corticosteroids have the advantage of being available in a wide range of potencies and vehicles in prescription and over-the-counter (OTC) formulations that can effectively address variations in severity that are common with the disease. Topical corticosteroids exert their effects on the cell nucleus, which leads to increased production of anti-inflammatory proteins, a decrease in transcription of proinflammatory cytokines, and possibly inhibition of the production of lipid mediators.

Topical corticosteroids are fast acting and highly effective anti-inflammatory agents but are limited in treating skin disease with a multifactorial pathogenesis because they lack multiple mechanisms to address more than one pathogenic factor. Mid- to high-potency agents are restrictive due to the potential for side effects, such as striae, telangiectasia, and rebound, especially with long-term use; even low-potency corticosteroids may cause adverse effects when used for long periods or on thin skin. Topical corticosteroids can be used for monotherapy or in combination with other medications but should be reserved for short-term therapy or flare. Treatment of seborrheic dermatitis on sensitive areas such as the face should be limited to low-potency agents, whenever possible.

Conversely, topical antifungal agents can be used for prolonged periods without the long-term adverse effects associated with topical corticosteroid treatment. These agents provide antifungal activity, and some specific products also provide anti-inflammatory activity. Like corticosteroids, they are available in a broad range of products and vehicles, which makes them useful for treatment of the body, face, and scalp.

It has long been recognized that *Malassezia* spp contribute to seborrheic dermatitis pathogenesis, but their exact role in disease pathogenesis is still being investigated. An early study showed that *Malassezia* spp comprised 86% of the total flora in individuals with seborrheic dermatitis, 74% of those with dandruff, and 46% of healthy volunteers; however, the condition is not always associated with increased yeast density. Various mechanisms have been advanced to explain the role of *Malassezia* in seborrheic dermatitis, including abnormal immune response, skin barrier defect, and inflammatory response in susceptible individuals to irritant free fatty acids released in response to *Malassezia* activity, but these and other theories are still being explored; nevertheless, topical antifungals are effective in the treatment of seborrheic dermatitis, and monotherapy and combination therapy, especially with a topical corticosteroid, are both commonly used treatment approaches. Topical antifungals work by reducing *Malassezia* proliferation—this means fewer fungi are available to trigger an inflammatory response, which improves disease signs and symptoms.

The current study assessed the efficacy, safety, and tolerability of a new prescription nonsteroidal medical device cream (Promiseb Topical Cream; Promius Pharma, LLC, Bridgewater, NJ) that has been cleared by the United States Food and Drug Administration (US FDA) and a commonly used low-potency corticosteroid cream (desonide 0.05%) for the treatment of facial seborrheic dermatitis. The nonsteroidal cream has antifungal and anti-inflammatory actions and uses emollients to relieve dry skin and facilitate healing. In addition, the nonsteroidal cream has no restrictions on age or duration of use, and it can be used on thin, sensitive areas such as the face. This contribution reports the results of the first study comparing this nonsteroidal cream with a low-potency corticosteroid.

**Methods**

This clinical study was performed in accordance with Good Clinical Practices and the Declaration of Helsinki (1996). The Institutional Review Board at each site approved the protocol, and written informed consent was obtained from each person in the study before study procedures were conducted.

The goal was to enroll between 60 and 80 participants aged 18 years or older, with each study site entering 5 to 20 individuals from the local area. Qualified participants had mild (score = 2) or moderate (score = 3) seborrheic dermatitis on the face as assessed by the investigator using the investigator global assessment (IGA) scale. Women of childbearing potential had to have a negative urine pregnancy test at baseline and practice a reliable method of contraception throughout the study.

Patients were excluded from enrolling for the following reasons: unwilling to stop treatment for dandruff or seborrheic dermatitis on the scalp; presented with severe (score = 4) seborrheic dermatitis on the face as assessed by the investigator; underwent treatment for seborrheic dermatitis or dandruff (face or scalp) with any topical antiseborrheic dermatitis or antidandruff product in the 14 days before baseline (day 0); chronic or active liver disease, renal impairment, severe facial acne or rosacea, or any other disease that would interfere with the study or place the person...
at undue risk; a known hypersensitivity to the ingredients of the products; and/or the use of any systemic medication or participation in a study of an investigational drug 30 days before baseline.

**Study design and intervention**

This was a randomized, active-controlled, investigator-blind, parallel-group study performed at eight centers. The nonsteroidal cream (Promiseb Topical Cream) was provided by Promius Pharma, LLC, Bridgewater, NJ. The low-potency corticosteroid cream was purchased from a United States wholesaler.

Participants were randomized to twice-daily treatment with the nonsteroidal cream or the corticosteroid cream for up to 28 days. Participants were instructed to massage the test formulation gently into the skin of all areas on the face exhibiting signs or symptoms of seborrheic dermatitis. If the condition cleared by day 14, the study drug was collected and the participant was told not to use any topical products on the previously treated areas until after the follow-up visit on day 28.

**Primary and secondary outcome assessments**

Investigators evaluated signs of seborrheic dermatitis on the face of each participant. Clinical determinations of erythema and scaling of treatment areas and IGA measurements were performed at baseline and at days 14 and 28. The IGA score was 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. Erythema, scaling, and pruritus were scored on a 5-point scale of 0 = none, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe. At each visit, the investigator asked participants to rate the severity of pruritus due to seborrheic dermatitis on the face present on that visit day. IGA was dichotomized as success (a score of 0 or 1) or failure (a score of 2, 3, or 4) at day 14 and day 28. The primary efficacy end point was the proportion of participants with IGA-rated success at either day 14 or day 28.

Secondary efficacy variables were IGA-rated success at day 14 and day 28 and erythema, scaling, pruritus, and IGA scores at days 14 and 28. In addition, the proportions of participants who cleared (score = 0) at day 14 and were still clear (score = 0) at day 28 were presented by treatment.

The overall safety score was the primary safety variable. On day 28, or earlier if the individual withdrew, the investigator graded overall safety using a scale of 0 to 3, where 0 = excellent (no signs of irritation during the study), 1 = good (slight signs of irritation during the study that resolved by the end of the study), 2 = fair (signs of irritation throughout the study), and 3 = poor (individual discontinued because of irritation). Irritation was defined as any sign or symptom of intolerance.

In addition, adverse events (AEs) were collected by spontaneous reports from participants, by questioning the participants, and by examination.

**Statistical analysis**

The intent-to-treat populations of the two groups were compared for treatment effect and within-group effect. Baseline data for the two groups were compared using a two-sided t test for age, the Fisher exact test for gender and race, and the Wilcoxon rank sum test for categoric data (scores). IGA was analyzed using the Fisher exact test to compare the proportion of participants with IGA-rated success (clear or almost clear) at day 14, day 28, and day 14 or 28, and the proportion of individuals who cleared at day 14 and remained clear at day 28. The Wilcoxon rank sum test was used to compare scores at day 14 and day 28. The Wilcoxon signed rank test was used in the within-group analyses of scores to determine the significance of changes from baseline and also to compare overall safety scores to determine significance of changes from baseline. The rates of AEs for the 2 treatment groups were compiled and compared using descriptive statistics.

**Results**

**Demographics and disposition**

The study enrolled 77 volunteers, with 39 in the corticosteroid cream group and 38 in the nonsteroidal cream group. Demographics were similar between groups and are summarized in Table 1. Most of the participants were men (73%), and the male/female ratio was similar between groups. Most volunteers were Caucasian (70%), followed by African American (22%) and Hispanic (8%). Of the 72 participants (94%) who completed the study, 38 (97%) were in the corticosteroid cream group, and 34 (89%) were in the nonsteroidal group (1 was lost to follow-up, 1 withdrew consent, and 1 withdrew because of a related AE).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 77)</th>
<th>Corticosteroid cream (n = 39)</th>
<th>Nonsteroidal cream (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>56 (73)</td>
<td>30 (77)</td>
<td>26 (68)</td>
</tr>
<tr>
<td>Women</td>
<td>21 (27)</td>
<td>9 (23)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Age, y Mean ± SD</td>
<td>51.9 ± 17.9</td>
<td>48.4 ± 17.4</td>
<td>55.5 ± 17.9</td>
</tr>
<tr>
<td>Median (P25, P75)</td>
<td>54.3</td>
<td>45.9</td>
<td>59.5</td>
</tr>
<tr>
<td>Min, max</td>
<td>21.1, 84.5</td>
<td>22.9, 83.0</td>
<td>21.1, 84.5</td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>54 (70)</td>
<td>23 (59)</td>
<td>31 (82)</td>
</tr>
<tr>
<td>African American</td>
<td>17 (22)</td>
<td>12 (31)</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6 (8)</td>
<td>4 (10)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

SD, standard deviation.
Efficacy

Efficacy results showed that individuals in both treatment groups demonstrated statistically significant reductions in IGA score from baseline to day 14 and day 28 (P < 0.0001; Figure 1). The mean IGA score did not differ significantly between groups at day 14 or day 28.

The primary efficacy end point was the proportion of participants with IGA-rated success (clear or almost clear) at day 14 or day 28, which was achieved by 92% of participants in the corticosteroid group and 85% in the nonsteroidal cream group. There were no significant differences between treatments in the proportion of participants with IGA success at day 14 or at day 28 in either treatment group (Figure 2).

Another component of efficacy assessments was the rate of relapse at day 28 (Figure 3). At day 14, 20% of participants in the nonsteroidal cream group were clear of disease signs and symptoms, and 39% in the corticosteroid cream group were clear. A significantly higher percentage of participants remained clear at day 28, after clearing at day 14, in the nonsteroidal cream group (71.4%) than in the corticosteroid cream group (14.3%; P = 0.0173), which means that 86% of participants in the corticosteroid group relapsed after day 14 (12 of 14 who were clear at day 14) compared with 29% (2 of 7 who were clear at day 14) in the nonsteroidal cream group.

Investigator assessments of erythema showed statistically significant within-group reductions from baseline in the erythema score at day 14 and day 28 (P < 0.0001; Figure 4) and no statistical differences between groups. A 2-point decrease in erythema scores was documented in 61% of the corticosteroid cream group and in 49% of the nonsteroidal cream groups at day 14, and in 51% and 66%, respectively, at day 28. The mean erythema score was reduced from 2.6 to 0.8 at day 28 for the nonsteroidal cream group and from 2.5 to 0.9 at day 28 for the corticosteroid cream group.

Similar patterns of improvement were observed for scaling. Analyses of scaling showed statistically significant within-group reductions from baseline to day 14 and day 28.
and no statistical differences between groups. At least a 2-point decrease in scaling was noted at day 14 in 71% of the corticosteroid and in 64% for nonsteroidal cream groups. Mean scaling score was reduced from 2.7 to 0.7 at day 28 for the nonsteroidal cream group and from 2.6 to 0.9 for the corticosteroid cream group.

Analyses of pruritus showed statistically significant within-group reductions from baseline to day 14 and day 28 ($P < 0.0001$; Figure 6) and no statistical differences between groups. At least a 2-point decrease in pruritus was noted in 47% for the corticosteroid and 49% for nonsteroidal cream groups at day 14, and 54% and 51%, respectively, at day 28. Mean pruritus scores were reduced from 2.1 to 0.7 at day 28 for the nonsteroidal cream group and from 1.8 to 0.6 for the corticosteroid cream group.

**Safety**

Both treatments demonstrated a similar safety profile. One case of mild irritation deemed related to treatment in the nonsteroidal cream group led to discontinuation, but it resolved with no sequelae, and one case of skin darkening on the nasolabial fold was considered possibly related to treatment in the corticosteroid cream group that was unresolved at study end. Overall, safety in both treatment groups was rated as excellent in more than 90% of participants in each treatment group, with no statistical difference between groups. An extension of the excellent safety and tolerability profiles of each treatment was a high rate of adherence to the study treatment regimen, with most individuals in each group being very compliant with treatment.

**Discussion**

The new nonsteroidal cream, which is approved by the US FDA, is indicated for the management and relief of the signs of symptoms of seborrhea and seborrheic dermatitis, such as itching, erythema, scaling, and pain. This novel topical cream contains an optimized combination of active ingredients that are beneficial in the treatment of seborrheic dermatitis. The nonsteroidal cream is formulated without fragrance, which likely minimizes the risk of contact dermatitis.

This study was designed around the expectation that the nonsteroidal cream would be similar in efficacy to that of the selected low-potency corticosteroid cream that is prescribed commonly for seborrheic dermatitis. It also was hoped that the use of the nonsteroidal cream would have the additional benefit of eliminating corticosteroid-associated side effects, including skin atrophy, steroid-induced acne, and tachyphylaxis, as well as rebound when treatment was stopped.

Both treatments demonstrated statistically significant reductions in the IGA score and rapid, effective relief of disease signs and symptoms. Treatment success rate, defined as an IGA score of 0 or 1, was approximately 90%, with no significant intergroup differences at day 14 or day 28. Participants in both groups achieved clinically important improvement.

The similarity between treatments also was evident in investigator assessments of reduction of disease signs. Most participants in both treatment groups experienced significant

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**Fig. 4 Reduction in Erythema.** A statistically significant reduction from baseline in the erythema score ($P < 0.0001$) was found for both study drugs, where 0 = none, 1 = slight, 2 = mild, and 3 = moderate.

**Fig. 5 Reduction in Scaling.** A statistically significant reduction from baseline in scaling score ($P < 0.0001$) was found for both study drugs, where 0 = none, 1 = slight, 2 = mild, and 3 = moderate.

**Fig. 6 Safety Profile.** A statistically significant reduction from baseline in the itching score ($P < 0.0001$) was found for both study drugs, where 0 = none, 1 = slight, 2 = mild, and 3 = moderate.
improvement (2-point reduction) in scaling and erythema of seborrheic dermatitis at both evaluation points.

Similar trends were seen in self-assessed improvement in pruritus, with significant within-group differences demonstrated in both treatment groups at the day 14 and day 28 evaluations. The similar efficacy of the corticosteroid and nonsteroidal creams extends to the safety profiles of these agents. The differences between groups were not statistically significant, with overall safety rated as excellent for more than 98% of the individuals in each treatment group.

Where study treatments diverged was in the rate of relapse. An earlier study assessed the duration of remission of various psoriasis therapies and found that relapse was a substantial treatment limitation with the use of topical corticosteroids. These observations were reconfirmed by the results of the current study, which showed that the nonsteroidal cream demonstrated a statistically significant and numerically important difference compared with the corticosteroid cream in duration of response, with disease relapse at day 28 in 12 of 14 (86%) participants who had cleared at day 14 in the corticosteroid group compared with two of seven (29%) in the nonsteroidal group. Although a small number of individuals in the nonsteroidal cream group were clear at day 14, these results suggest that the nonsteroidal cream may reduce the colonization of Malassezia spp and thus the trigger for the inflammatory response, which may be the reason for the lower relapse rate of the nonsteroidal cream.

Conclusions

These findings are important for the patient with seborrheic dermatitis who needs a variety of treatments to address the different presentations of the disease. The results of this study support the use of the nonsteroidal cream as monotherapy and in conjunction with a topical corticosteroid in the seborrheic dermatitis regimen.

References