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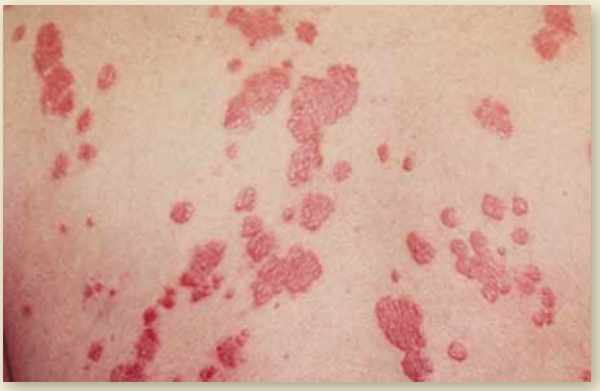
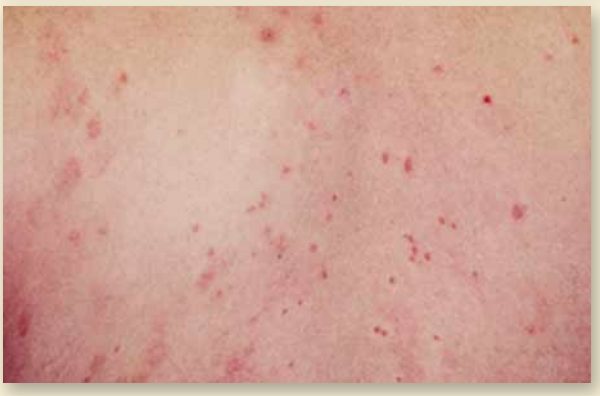
Clearing Psoriasis: The Role of a Novel 2-Compound Ointment as First-Line Therapy

- Current Topical Therapies for Psoriasis
- Efficacy of a Novel 2-Compound Ointment
- Safety Profile of a Novel 2-Compound Ointment
- Role of a 2-Compound Ointment in the Treatment Armamentarium for Psoriasis Vulgaris





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TARGET AUDIENCE

This activity is intended for dermatologists who are involved in the treatment of patients with psoriasis.

FACULTY AND UNAPPROVED/OFF-LABEL USE DISCLOSURES

Craig Leonardi, MD, is a consultant for Abbott Laboratories, Amgen, Inc., Centocor, Inc., and Genentech, Inc. He has been an investigator for Abbott, Allergan, Inc., Altana, Inc., Amgen, Astellas Pharma US, Bristol-Myers Squibb, Centocor, CombinatoRx, Galderma Laboratories, L.P., Genentech, Novartis Pharmaceuticals, RTL, Schering-Plough Corporation, 3M Pharmaceuticals, and Vitae Pharmaceuticals. He is on the speakers' bureau for Abbott, Amgen, Centocor, Genentech, and Warner Chilcott (US), Inc.

Jerry Bagel, MD, speaks for Abbott, Amgen, Astellas, Genentech, Novartis, and Warner Chilcott. He is an investigator for Amgen, Astellas, Centocor, and Galderma.

Mark Lebwohl, MD, is a consultant for or has pending consulting agreements for Abbott, Amgen, Astellas, Bristol-Myers Squibb, Centocor, Connetics Pharmaceuticals, Galderma, Genentech, Novartis, Pfizer, Inc., 3M, and Warner Chilcott. In the last 12 months, he has served as a speaker for Abbott, Amgen, Astellas, Centocor, Chester Valley, Connetics, Galderma, Genentech, Novartis, PharmaDerm, 3M, and Warner Chilcott.

Linda Stein Gold, MD, is a principal investigator, consultant, and member of the speakers' bureaus for Connetics, Galderma, and Warner Chilcott. She is a member of the speakers' bureau and a consultant for Genentech, and she is also a principal investigator for Astellas.

The participants discuss using the 2-compound ointment beyond the 4 weeks indicated by the product labeling.

Introduction

Associated with significant morbidity and impaired quality of life, chronic plaque psoriasis afflicts 2% to 3% of the population in the United States and Europe.[1,2] The pathogenesis of psoriasis involves inflammation and abnormalities of cutaneous proliferation and differentiation. Because of significant morbidity and even mortality associated with psoriasis, treatment of this chronic inflammatory and proliferative disease has significant benefits beyond cosmesis. Predominant treatments, which many patients perceive as inconvenient, slow-acting, toxic, and/or ineffective, are not meeting the therapeutic goals for as many as 85% of psoriasis patients.[3]

While systemic therapy, phototherapy, and biologics are used to treat some patients, approximately 80% of psoriasis patients will receive topical therapy (**Figure** 1 on page 4).[4-6] Studies of topical corticosteroids and calcipotriene (Dovonex®, Warner Chilcott (US), Inc., Rockaway, N.J.) have proven them to be effective, when used within label, in clearing plaque psoriasis without causing significant cutaneous atrophy or skin irritation. Other topical treatments include keratolytic agents, topical tars, and retinoids.[6]

Since April 2006, calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment (Taclonex®, Warner Chilcott (US), Inc., Rockaway, N.J.) has been available in the United States for the treatment of psoriasis vulgaris in adults 18 years of age and above. The novel 2-compound ointment has a number of advantages as initial therapy for patients with mild, moderate, or severe disease, and it has been studied as maintenance therapy for up to 52 weeks.[7,8]

Based on a presentation delivered by Craig Leonardi, MD, at a Skin Disease Education Foundation meeting in November 2006, a roundtable was held among experts in psoriasis treatment to discuss approaches to optimize topical treatment of patients with psoriasis and to evaluate the role of the 2-compound ointment in the therapeutic landscape. The conference provided an opportunity for Craig Leonardi, MD, Jerry Bagel, MD, Mark Lebwohl, MD, and Linda Stein Gold, MD, to share their initial clinical experiences and to describe where they position the 2-compound ointment in their treatment armamentarium. This supplement summarizes the data reviewed and the experiences shared during this meeting.

Current Topical Therapies for Psoriasis

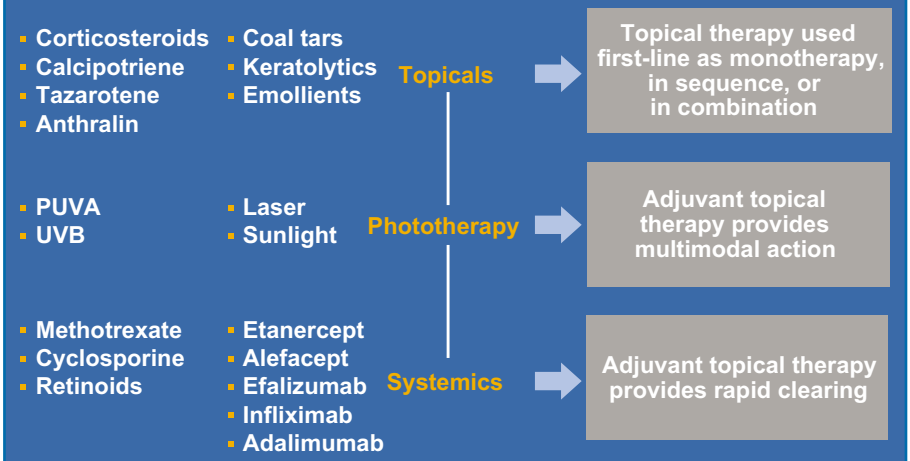
Currently, most physicians in the United States and Europe prescribe topical formulations of superpotent corticosteroids and calcipotriene, respectively, to treat psoriasis. In the United States, 79% of patients are prescribed topical steroids of any class; of those, 58% receive a class 1 (superpotent) agent.[4] In Europe, the most commonly prescribed topical therapy has been calcipotriene.[9] Often, these agents are used in combination with each other or with other therapeutic options such as phototherapy and biologics. Prior to the introduction of the 2-compound ointment, the roundtable participants used a variety of topical treatments alone and in sequential, rotational, and other combination regimens; the most frequently prescribed topicals included halobetasol, clobetasol, salicylic acid, tazarotene (Tazorac®, Allergan, Inc., Irvine, Calif.), and calcipotriene, among others. The panel discussed some of these topical therapies as well as the pros and cons associated with the most widely used sequential and combination therapies.

For all participants, the once-daily 2-compound ointment has generally replaced the topical regimens they previously employed.

"All of my psoriasis patients use topical therapy … whether they have localized or very extensive disease. Even patients who are on systemics or biologic therapy still have some resistant lesions (that require topical treatment)."
—Linda Stein Gold, MD

Mark Lebwohl, MD: (Before the 2-compound ointment), probably the most common regimen that I used was a combination of halobetasol and calcipotriene. It was a regimen where patients used both for approximately 2 weeks and then would use the calcipotriene every day and the halobetasol on weekends only.

FIGURE 1. Topical Therapy Is Appropriate for Psoriasis Regardless of Severity



PUVA = psoralen plus ultraviolet A light; UVB = ultraviolet B light.
Source: Stern RS. Psoriasis. *Lancet.* 1997;350:349-353.

Linda Stein Gold, MD: I agree with Dr Lebwohl. He was involved in a paper that explained the use of the combination of calcipotriene and halobetasol, and it gave us a step-by-step outline of how to use it effectively. This was adopted by a number of dermatologists, and I generally used potent and superpotent steroids, usually in combination with calcipotriene. I also use tazarotene, but I use it in combination with a topical steroid to minimize irritation.

Jerry Bagel, MD: Before I used the 2-compound ointment, I would prescribe 6% salicylic acid in triamcinolone ointment at night for patients prior to coming in for phototherapy. I used a lot of salicylic acid and compounded it with topical steroids. For localized areas, I used the regimen that Dr Lebwohl described, as well.

"Now, I rarely prescribe calcipotriene and halobetasol or calcipotriene and clobetasol; rather, I prescribe the 2-compound ointment once a day."
—Jerry Bagel, MD

Craig Leonardi, MD: Dr Lebwohl did teach us about calcipotriene and halobetasol, and I think many of us took that to heart. But the regimen was complicated. Typically, I'd have my patients apply both medicines twice a day for a month, and then at that point I would change them over to using just calcipotriene 7 days a week, twice a day, and halobetasol on the weekends in combination with calcipotriene. I would instruct the patients to mix equal amounts of these products in their palms and put them on one time, each twice a day. Despite the effec-

tiveness of this treatment regimen in trial settings, I think I always knew that real-world compliance was limited by the regimen.

"The 2-compound ointment is appropriate therapy for patients with mild, moderate, or severe disease."

—Craig Leonardi, MD

Effectiveness of Topical Treatments

The effectiveness of a drug is a function of its efficacy (as determined from randomized controlled trials), its safety, and patients' compliance (**Figure 2**).[10,11] In the opinion of the participants, time to onset of action, plus compliance, seem to be the major factors influencing effectiveness. They acknowledged that studies showing underreporting of compliance and decreasing compliance over time are mirrored to varying degrees in their clinics.

Linda Stein Gold, MD: I think our most motivated patients who followed the regimen appropriately saw great efficacy, but we relied on our patients to do what we were telling them to do. That wasn't always happening. I think frequently the patients would not have the time or expend the effort to do it. Often, they would end up only using their superpotent steroid, and the calcipotriene would not always get used.

Craig Leonardi, MD: I actually had several patients ask the pharmacists to mix the medications together for them as they picked it up. They were mixing calcipotriene and halobetasol together, and then using that combination for a month or two. Of course, we know that these drugs are chemically unstable when mixed in this way. It was a creative approach but definitely not what we wanted.

Mark Lebwohl, MD: When you mix two agents together, you take 0.005% calcipotriene and mix it with the 0.05% concentration of halobetasol. You're going to end up with an end product that is 0.0025% calcipotriene and 0.025% halobetasol. By diluting the ingredient with the other product, you're essentially ending up with a final product that is half as concentrated.

With the 2-compound ointment, you now have the full concentrations of both calcipotriene and betamethasone in the final product. Concentration certainly will impact penetration because of partition coefficients, because of the amount of drug that a given area of skin is exposed to. You would expect higher concentrations to penetrate more and to be more effective.

Craig Leonardi, MD: The most important issues with topical therapy involve compliance and response time. Many studies have shown that patients are unable or unwilling to comply with BID topical schedules, especially when large areas are involved. Furthermore, compliance is always enhanced when the treatment effects are seen early.

"With the 2-compound ointment, you now have the full concentrations of both calcipotriene and betamethasone in the final product. . . . You would expect higher concentrations to penetrate more and to be more effective."

—Mark Lebwohl, MD

Linda Stein Gold, MD: In general, the simpler we keep the regimen for patients, the more likely it is that they'll actually do what we ask them to do once they get home. Treatment regimens can be very confusing, and I think time is certainly an element. Patients like to have a quick treatment regimen. They like to do something quickly and run out the door. Keeping it simple, keeping it once a day, certainly improves the likelihood that patients are going to be compliant with their medications. There was a study that looked at the numbers of prescriptions that were refilled when we prescribed potent steroids and calcipotriene, and, over time, the calcipotriene prescriptions were not being refilled. Patients were starting out with it, but eventually were just refilling prescriptions for the potent steroid.

FIGURE 2. Compliance With Topical Therapies

Effectiveness = Compliance + Efficacy + Safety

- **Factors that may impair compliance with topical therapies**
  - **Complexity of regimen (sequential, rotational)**
  - **Efficacy**
  - **Cosmetic considerations**
  - **Time for application**
  - **Time to achieve improvement**
  - **Lack of education**
  - **Adverse events**

Sources: Koehler AM, Maibach HI. Electronic monitoring in medication adherence measurement. Implications for dermatology. *Am J Clin Dermatol.* 2001;2:7-12; Kane SV. Systematic review: Adherence issues in the treatment of ulcerative colitis. *Aliment Pharmacol Ther.* 2006;23:577-585.

Jerry Bagel, MD: Dermatologists prescribe calcipotriene ointment and halobetasol ointment, or even clobetasol ointment, twice a day, two times a week, and then tell patients to switch on Mondays through Fridays. It's a lot of explanation from the physician. We write the prescriptions and give patients another paper explaining how to do it, and they're still not completely sure of what to do. After 2 weeks, sometimes the instructions are lost. It's a very complex mechanism, and once-a-day treatment is much simpler for the physician to explain and for the patients to understand and actually implement.

"Keeping it simple, keeping it once a day, certainly improves the likelihood that patients are going to be compliant with their medications."
—Linda Stein Gold, MD

Craig Leonardi, MD: There was a lot of room for confusion. Sometimes I'd find patients using calcipotriene on the weekends only, and halobetasol 7 days a week. Or, using both medications on just the weekends. By contrast, the regimen is once a day with the 2-compound ointment, and it's an ointment vehicle. It's certainly the form that works the best according to our understanding of how these drugs are delivered into the skin.

Because the 2-compound ointment is used once a day, my patients put it on at bedtime, and then it can stay put overnight. The ointment doesn't rub off on their work clothes, and the treatment regimen does not interfere with their ability to jump-start their day. To me, a once-a-day regimen is all about convenience, and I think that's what drives my selection process.

Linda Stein Gold, MD: All of my psoriasis patients use topical therapy. I feel that everybody needs some topical treatment, whether they have localized or very extensive disease. Even patients who are on systemics or biologic therapy still have some resistant lesions. Sometimes I use it also at the initiation of systemic therapy while we're waiting for those other agents to have an effect.

Jerry Bagel, MD: Topical therapies are utilized in almost all cases of psoriasis. I can't count the number of times that I wrote this prescription: calcipotriene ointment, 0.005% BID, and halobetasol ointment BID for 2 weeks, to be followed by calcipotriene ointment BID Monday through Friday, halobetasol ointment BID on the weekends for 6 weeks, then to use halobetasol ointment on the weekends alone.

I then had to explain that to all of my patients. I was thankful enough that I had that regimen available, because it worked, but how many people want to wake up in the morning and put ointments on? Nobody. And then go to work or go to school? No. People did not want to do that.

Some of my patients have been so frustrated that they'll never use topical therapy. When I can convince them that they only have to use the 2-compound ointment once a day, they're willing to try it. Some of them have been discouraged by the 23 minutes a day they spend applying two medications twice a day, but they can be re-educated as to the benefits of topical therapy if it requires application only once a day.

Now, I rarely prescribe calcipotriene and halobetasol or calcipotriene and clobetasol; rather, I prescribe the 2-compound ointment once a day. Similarly, I rarely prescribe salicylic acid compounded in cortisone ointment prior to phototherapy; I just use the 2-compound ointment.

Craig Leonardi, MD: Since the introduction of the 2-compound ointment, I tend to give topical therapy a chance, even in patients whom I might have treated immediately with a systemic or a biologic agent in the past. ■

"The most important issues with topical therapy involve compliance and response time. … My patients put (the 2-compound ointment) on at bedtime, and … (it) does not interfere with their ability to jump-start their day. To me, a once-a-day regimen is all about convenience, and I think that's what drives my selection process."
—Craig Leonardi, MD

PANEL CONSENSUS: Current Topical Therapies for Psoriasis

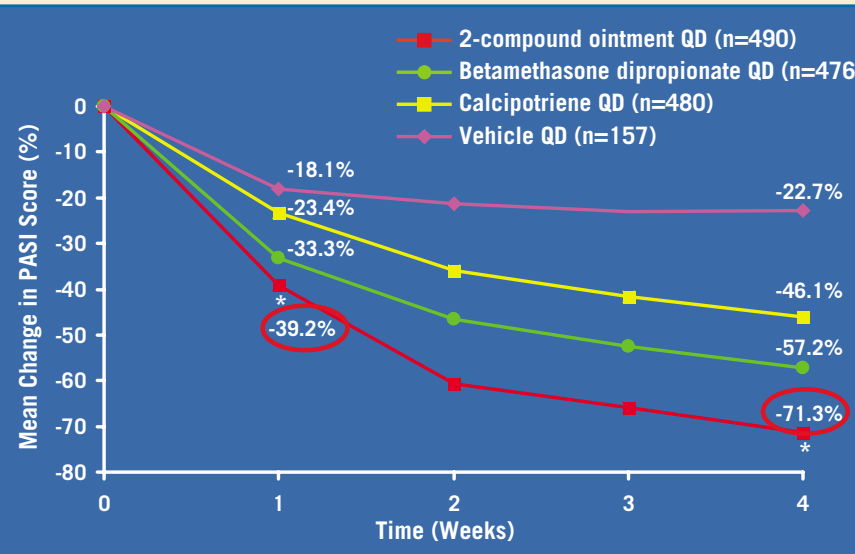
- Psoriasis patients, regardless of disease severity, require topical treatment.
- Patients are most compliant when treatment regimens are convenient, simple, and fast-acting.
- Sequential or combination use of calcipotriene and a steroid has been the most effective topical regimen, but it is often too complex or inconvenient for acceptable compliance.
- Once-daily treatment with the 2-compound ointment has generally replaced the previously prescribed topical regimens.

Efficacy of a Novel 2-Compound Ointment

The novel 2-compound ointment combines calcipotriene 0.005% and betamethasone dipropionate 0.064% in an anhydrous vehicle (**Figures 3** and 4). Its efficacy and safety have been evaluated in 6 large, multicenter clinical trials.[12] The results of these trials indicated that patients with all levels of psoriasis severity treated with the 2-compound ointment demonstrated significantly greater and more rapid improvement in the Psoriasis Area and Severity Index (PASI) scores, compared with patients treated with calcipotriene or betamethasone dipropionate alone (**Figure 5** and **Figure 6** on page 8).[13,14] More patients treated with the 2-compound ointment also achieved absence and/or clearing of disease (**Figure 7** on page 8). In addition, these clinical trials demonstrated consistent results (**Figure 8** on page 9)[12] that the participants have seen reproduced in their own patients.

Drs Leonardi, Bagel, Lebwohl, and Stein Gold reviewed the clinical trial data on the 2-compound ointment before sharing their own experiences treating patients with this product.

FIGURE 5. A 2-Compound Ointment: Greater and More Rapid PASI Improvement Than Monotherapy



PASI = Psoriasis Area and Severity Index.

*$p<0.001$ for betamethasone/calcipotriene ointment vs. vehicle, betamethasone dipropionate, and calcipotriene.

Source: Kaufmann R, Bibby AJ, Bissonnette R, et al. A new calcipotriol/bethamethasone dipropionate formulation (Daivobet™) is an effective once-daily treatment for psoriasis vulgaris. *Dermatology.* 2002; 205:389-393. Used by permission. Copyright S. Karger AG, Basel, Switzerland.

Jerry Bagel, MD: I think the dual mechanism of action of the 2-compound ointment works well because I don't get any phone calls about irritation from people using the 2-compound ointment. The topical steroid effect minimizes any irritation from calcipotriene, which is ideal for the patient. Patients don't experience irritation, don't get upset over their treatment, and don't

FIGURE 3. The Novel Formulation Allows the Product to Be a Full-Strength 2-Compound Product, Not Two Diluted Compounds in One Product

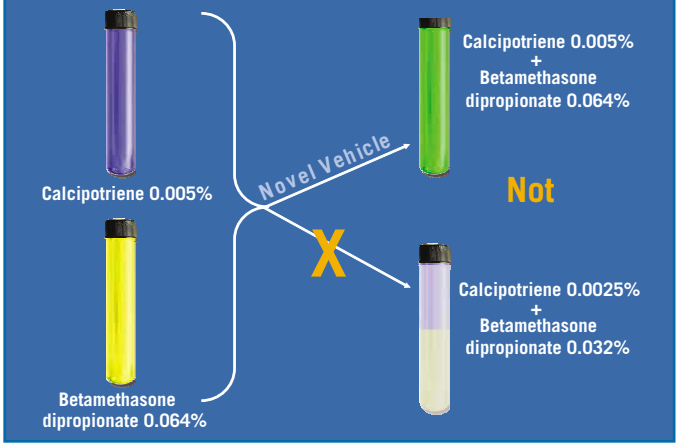
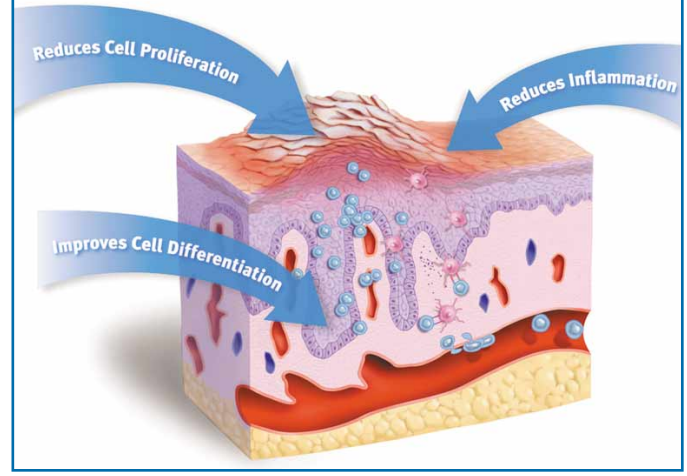


FIGURE 4. 2-Compound Ointment Simultaneously Targets Multiple Disease Pathways of Psoriasis



call me because they're angry. It's a win-win situation.

"You get better efficacy than you would with either medication alone, and that's important to patients as well—not only the convenience but additional improvement for the same amount of effort."
—Craig Leonardi, MD

Mark Lebwohl, MD: The dual mechanism of action also explains why the drug works faster than either calcipotriene or betamethasone dipropionate.

Craig Leonardi, MD: You get better efficacy than you would with either medication alone, and that's what's important to the patients as well—not only the convenience but additional improvement for the same amount of effort.

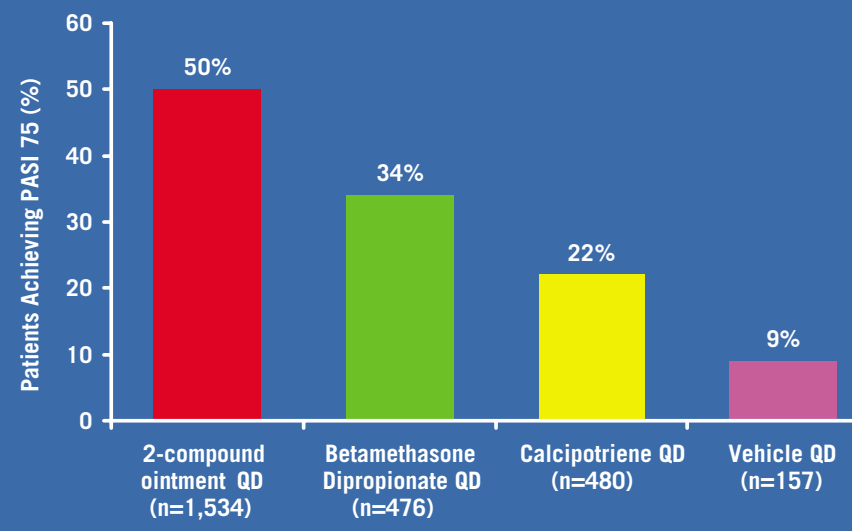
"When I've prescribed the 2-compound ointment to patients who have severe disease, within 1 week they are thrilled."
—Mark Lebwohl, MD

2-Compound Ointment: Efficacy in Clinical Trials

Jerry Bagel, MD: I saw the data first at the American Academy of Dermatology meeting in March 2006, in San Francisco, and I was very impressed. Over 70% improvement in 4 weeks was striking. I also saw PASI 75 data at 4 weeks that were clearly significant, 50%, and I thought the product would work. When I heard the drug was soon to be available, I thought it would be very effective.

Craig Leonardi, MD: The data show that the 2-compound ointment produces similar results to sequential therapy, and compliance can be so much better since it requires only once-daily dosing.

FIGURE 6. PASI 75 Achieved With Once-Daily 2-Compound Ointment After 4 Weeks of Treatment*

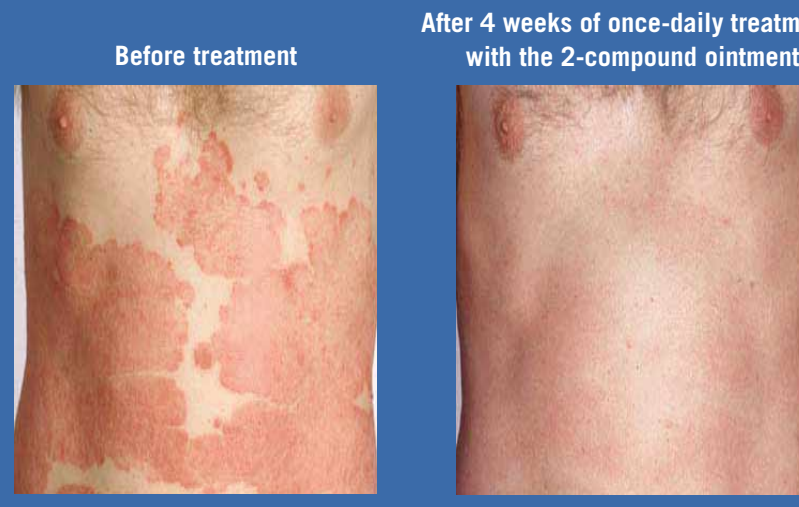


PASI 75 = at least 75% improvement in Psoriasis Area and Severity Index (PASI) from baseline.

*Pooled data from four clinical trials. All treatments applied once daily for four weeks.

Source: Anstey A, Bibby AJ. A pooled analysis of studies with a new calcipotriene/betamethasone two-compound product shows effective and rapid response in psoriasis vulgaris. *J Eur Acad Dermatol Venereol*. 2004;18 (suppl 2):193-557. Used by permission.

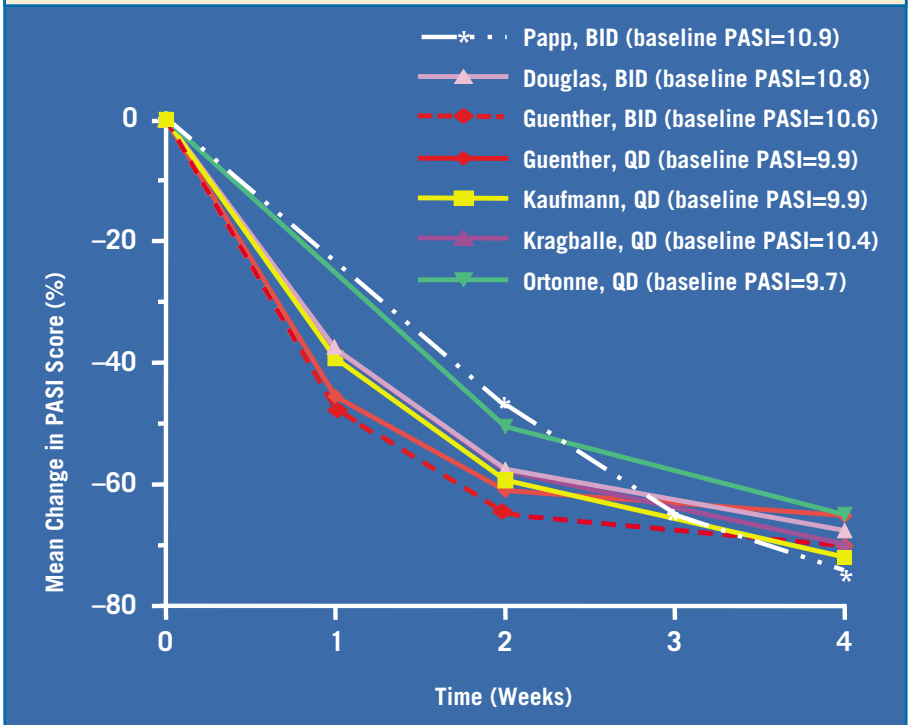
FIGURE 7. Before and After Results of 4 Weeks of Once-Daily Therapy With the 2-Compound Ointment in a Patient With Extensive Psoriasis Involving the Chest and Abdomen



Example of treatment response to the once-daily 2-compound ointment.
Photos courtesy of LEO Pharma A/S and Dr Hugo Boonen, BE.

Mark Lebwohl, MD: The numbers are dramatic. What I'll say about the 1-week data is that when I've prescribed

FIGURE 8. Consistency of Clinical Study Results of 6 Controlled Trials*



*2-compound ointment: BID and QD administration yielded similar results.
PASI = Psoriasis Area and Severity Index.

Source: Kragballe K, van de Kerkhof PC. Consistency of data in six phase III clinical studies of a two-compound product containing calcipotriol and betamethasone dipropionate ointment for the treatment of psoriasis. *J Eur Acad Dermatol Venereol.* 2006;20:39-44. Used by permission. Copyright Blackwell Publishing, Oxford, UK.

the 2-compound ointment to patients who have severe disease, within 1 week they are thrilled. Just today I had a patient who decided not to continue with the systemic therapy because he got such a good response from the 2-compound ointment. That's unusual; most of the patients who need systemic therapy, need systemic therapy, but there are some patients who do very well just with topical therapy, even patients with severe disease.

The 1-week data were impressive to me, but the consistency data are the most dramatic because you know the data are accurate. The short-term data are accurate; the overall reduction in PASI score is accurate. What you're seeing in one clinical trial, you're seeing in every clinical trial. The 2-compound ointment works very quickly, and it works quite well.

"You know the data are accurate…What you're seeing in one clinical trial, you're seeing in every clinical trial. The 2-compound ointment works very quickly, and it works quite well."
—Mark Lebwohl, MD

Linda Stein Gold, MD: I agree. I had the opportunity to do one of the clinical trials before the drug was approved by the US Food and Drug Administration, and I didn't have any great expectations for the drug. I was not really sure what benefit this drug would have, other than convenience, and my study subjects had all used calcipotriene and halobetasol in the past. I really didn't know what to expect, but the efficacy has been dramatic.

I had a difficult case. The patient had been on systemic agents in the past and his schedule did not permit him to undergo phototherapy. He had 30% body surface area involvement and had participated in one of the clinical trials of the 2-compound ointment with complete clearance after 4 weeks. In the past, the patient had been treated with halobetasol and calcipotriene without the same dramatic effect. He was not interested in any type of injection therapy. Once the 2-compound ointment was released, I re-treated him with it. In 2 weeks he came back with marked improvement in his plaques. Over 4 weeks, he just got better and better, and by week 6, he was virtually clear. The improvement with the 2-compound ointment completely exceeded my expectations, even with thick, severe localized plaques on the knees and shins.

Craig Leonardi, MD: When I first saw the data, I thought that if I could get those results with a class 2 steroid, I'd

PANEL CONSENSUS: Efficacy of the 2-Compound Ointment

- Consistent clinical trial data demonstrate that the 2-compound ointment clears psoriasis quickly and effectively in patients with mild to moderate psoriasis.
- The success of the 2-compound ointment in clinical trials has been reproduced in practice, as patients find it easy to use and results are achieved as early as 1 week.
- Even patients with extensive or severe disease can benefit from 2-compound ointment treatment. For some patients, the topical therapy replaces the need for other forms of treatment.

welcome the opportunity to avoid the adverse events of a superpotent steroid and have the simplicity of a once-daily application. The 2-compound ointment eliminates the mixing, the dilution, and the compliance issues with sequential therapy.

With extensive disease, I think you're getting into the area where topical monotherapy used to end and a systemic begins. Still, some patients with moderate psoriasis respond well to the 2-compound ointment used as monotherapy. I've had situations where a delay in starting a biologic has created an opportunity for the 2-compound ointment to "stand tall" as the sole treatment. In more than a few patients, the drug has rendered improvement to a point where a systemic approach is no longer required.

Mark Lebwohl, MD: I've given a few patients the option of trying two different topical therapies for their bilateral disease: a superpotent steroid like halobetasol plus calcipotriene on one side, and the 2-compound ointment on the other. Even though the response is similar, the patients tend to stop the combination regimen after a short time because the 2-compound ointment is much more convenient. ■

"I'd welcome the opportunity to avoid the adverse events of a superpotent steroid and have the simplicity of a once-daily application."

—Craig Leonardi, MD

Safety Profile of a Novel 2-Compound Ointment

After commenting on the efficacy of the 2-compound ointment in clinical trials and in specific case studies, the roundtable participants addressed three potential adverse events that might be associated with the pharmacologic properties of betamethasone and calcipotriene: (1) cutaneous atrophy, (2) hypothalamic-pituitary-adrenal (HPA)-axis suppression, and (3) cutaneous irritation.

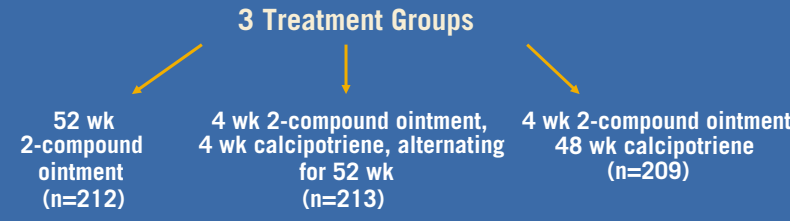
The 2-compound ointment is categorized as a class 2 (potent) steroid.[15] The strength of corticosteroids is generally determined from the vasoconstriction, determined visually or by means of an instrument, that results when a specific quantity of the drug is applied to a defined area of skin.[16] The potency can also be assessed by other methods, such as the ability of the drug to inhibit ultraviolet light-induced erythema and the cutaneous atrophy that results when the drug is applied under occlusion. The pharmacologic differences are a function of the vehicles used to compound the drug. Betamethasone dipropionate can exhibit the properties of either a class 1 or a class 2 corticosteroid.

Craig Leonardi, MD: I think the advantage of using a class 2 steroid is that if you have to use this drug in a long-term setting (outside the labeled indication), you have far less risk of running into the usual problems we see with class 1 steroids, which would include atrophy and tachyphylaxis.

There are advantages to reducing the strength of the steroid. When I was in training, the class 1 steroids first emerged. I saw patients admitted to the University of Miami who had gotten the superpotent steroids abroad and after extensive use with occlusion had developed significant systemic side effects. These patients were using class 1 steroids aggressively and in addition to adrenal axis suppression, their skin was having problems with striae and atrophy as well. Any time we can get improved efficacy with a lower-class steroid, we're way ahead of the game.

FIGURE 9. 2-Compound Ointment: 52-Week Study Design*

- **Study design**
  - Psoriasis of at least moderate severity† as indicated by the Investigators' Global Assessment
  - Hospital outpatients or patients seen in dermatology private practice



*All treatments used once daily, intermittently, on an as-needed basis, for up to 52 weeks. Safety and efficacy assessments conducted every 4 weeks. Safety events were adjudicated by an independent panel of 3 dermatologists blinded to all treatments.

†Moderate severity defined as red lesions with moderate thickness and scaliness.

Source: Kragballe K, Austad J, Barnes L, et al. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product (Dovobet®/Daivobet®/Talconex®) in the treatment of psoriasis vulgaris. *Br J Dermatol*. 2006;154(6):1155-1160.

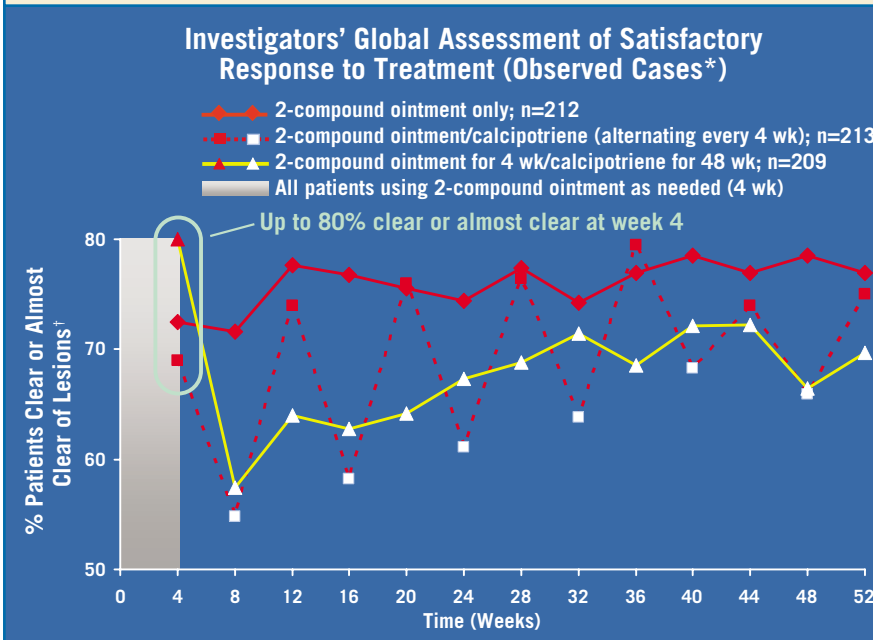
"Having a class 2 steroid as opposed to a superpotent steroid gives us a little more of a cushion of safety."
—Linda Stein Gold, MD

Jerry Bagel, MD: I agree with that, but I still take into account the number of refills I give and make sure that they're based on the body surface area I'm treating. I'm keeping track of how many tubes they're actually using in between appointments when I see them.

Long-Term Safety: 52-Week Trial and Clinical Experience

Recognizing that psoriasis is a chronic disease that often requires long-term treatment beyond 4 or 8 weeks, Kragballe et al conducted a 52-week study of the 2-compound ointment in patients with moderate to severe psoriasis (**Figure 9**).[7,8] Patients were randomized to use the 2-compound ointment, the 2-compound ointment alternating with calcipotriene every 4 weeks, or the 2-compound ointment for 4 weeks followed by calcipotriene for 48 weeks, once a day, intermittently, as needed for up to 52 weeks (**Figure 10** on page 12).[8] The patients revisited the investigators every 4

FIGURE 10. 2-Compound Ointment QD: Consistent Long-Term Efficacy



*Observed cases: Analysis of only patients with available data at each time point.
†Satisfactory response.

Source: Kragballe K, Austad J, Barnes L, et al. Efficacy results of a 52-week randomised, double-blind safety study of a calcipotriol/betamethasone dipropionate two-compound product (Daivobet®/Dovobet®) in the treatment of psoriasis vulgaris. *Dermatology.* 2006;213:319-26.

TABLE 1. Adverse Events Commonly Associated With Long-Term Corticosteroid Use, Identified in the 52-Week Trial of the 2-Compound Ointment*

	2-compound ointment only (52 wk; n=207)†		2-compound ointment/ calcipotriene (alt. 4 wk; n=213)†		2-compound ointment 4 wk/calcipotriene 48 wk (n=206)†	
Event	**n**	**%**	**n**	**%**	**n**	**%**
Adrenal insufficiency	0	0.0	0	0.0	1	0.5
Cellulitis	0	0.0	0	0.0	1	0.5
Ecchymosis	1	0.5	0	0.0	0	0.0
Folliculitis	3	1.4	1	0.5	0	0.0
Furuncle	0	0.0	2	0.9	0	0.0
Hypertrichosis	0	0.0	0	0.0	1	0.5
Purpura	1	0.5	0	0.0	1	0.5
Rash, pustular	0	0.0	1	0.5	0	0.0
Skin atrophy	4	1.9	1	0.5	2	1.0
Skin depigmentation	2	1.0	0	0.0	0	0.0
Skin papilloma	0	0.0	1	0.5	0	0.0
Skin striae	0	0.0	1	0.5	0	0.0
Total no. of events	11		7		6	
Total no. of patients	10	4.8	6	2.8	6	2.9

*Adverse events were identified by an independent panel of three dermatologists blinded to all treatments.
†No statistically significant differences were found between treatment groups.

Source: Kragballe K, Austad J, Barnes L, et al. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product (Dovobet®/Daivobet®/Talconex®) in the treatment of psoriasis vulgaris. *Br J Dermatol.* 2006;154(6):1155-1160. Used by permission. Copyright Blackwell Publishing, Oxford, UK.

weeks to assess efficacy and undergo independent adjudication of adverse events.[7,8] In the 52-week safety study, cutaneous atrophy was identified by the panel in four patients (1.9%) in the 2-compound ointment group, in one patient (0.5%) in the alternating 2-compound ointment and calcipotriene group, and in two patients (1.0%) in the calcipotriene group (**Table 1**).[7] The study demonstrated no clinical evidence of corticosteroid-induced HPA-axis suppression. In a subset of 19 patients who underwent adrenal function testing, a single case of adrenal insufficiency was identified in a patient who had received 11 months of calcipotriene monotherapy.[7] This was judged not to be related to the initial 4 weeks of treatment with the 2-compound ointment.[7]

The Prescribing Information for the 2-compound ointment states that the drug is indicated for the topical treatment of adults 18 years of age and above with psoriasis vulgaris for up to 4 weeks.[15] The patient information section of the package insert instructs patients not to use the ointment for more than 4 weeks "unless prescribed by your doctor."[15] All of the participants treat patients with the 2-compound ointment once daily for longer than 4 weeks as needed, when long-term therapy is necessary to treat the disease. However, the participants were careful to emphasize that periodic re-evaluation of patients is important to monitor and identify adverse events before they become clinically significant.

Craig Leonardi, MD: I think that 52 weeks is the longest study of a topical treatment for psoriasis.

Linda Stein Gold, MD: I don't know of another year-long study. The thing I like about this trial is that the drug administration mimics how people apply treatments in real life. They clear up; they stop using it. The as-needed application really shows how this drug

will affect people if they're using the 2-compound ointment as maintenance therapy.

Jerry Bagel, MD: I feel much more comfortable about using the 2-compound ointment over other steroids or calcipotriene for long-term use, but I still keep track of how much I prescribe. It's still a potent steroid. It's not a superpotent steroid, but it's strong, and you need to observe how much you're using.

Linda Stein Gold, MD: I agree with that. I like to see my patients on a fairly regular schedule.

Mark Lebwohl, MD: I think that last point is important. You do have to actually bring the patient back in for follow-up. The length of time between visits obviously depends on what part of the body you're treating. I often write the prescription for the 2-compound ointment as I did with halobetasol, for use daily before bedtime for 4 weeks, and then weekends only. However, if the psoriasis is affecting the palms or soles, which are thick-skinned areas that seldom experience side effects from steroid use, I'll have patients use the 2-compound ointment every evening for a longer period of time. In that situation, I'm much less worried about getting steroidal side effects on the palms and soles. A little bit of judgment is needed, but if you prescribe the ointment for use on the body, I think that you need to bring patients back no later than 3 months into therapy.

PANEL CONSENSUS: Safety of the 2-Compound Ointment

- Consisting of betamethasone dipropionate, a class 2 steroid, and calcipotriene, the 2-compound ointment ensures a very low incidence of steroid-related adverse events without sacrificing efficacy.
- Clinical trials and clinicians' experiences suggest that the 2-compound ointment is safe to use as initial therapy and then intermittently for maintenance treatment with appropriate physician supervision.

"Both products in the 2-compound ointment are cancelling out each other's well-documented adverse events. That's impressive, and it just confirms that the two products together are better than either one alone."

—Jerry Bagel, MD

Linda Stein Gold, MD: I do a very similar thing. I always see the patients again at 4 weeks. If they have some resistant lesions, I'm fairly comfortable going ahead and having them continue to treat those lesions daily as needed. Then, once the areas are clear, I ask them to use a maintenance regimen twice a week.

Mark Lebwohl, MD: The cutaneous events in the study were exactly what you would expect with these medications. There weren't any significant differences between the groups in cutaneous events.

Linda Stein Gold, MD: In addition, there was no evidence of steroid-induced HPA-axis suppression in the subset of patients in the 2-compound ointment group whose adrenal function was tested.

Jerry Bagel, MD: The fact that there were no cases of striae in the 2-compound ointment-only group is a surprise. The betamethasone in the ointment decreases inflammation, so that explains why you see less irritation than with calcipotriene monotherapy. Both products in the 2-compound ointment are cancelling out each other's well-documented adverse events. That's impressive, and it just confirms that the two products together are better than either one alone. ■

"I don't get any phone calls about irritation from people using the 2-compound ointment. . . . Patients don't experience irritation, don't get upset over their treatment, and don't call me because they're angry. It's a win-win situation."

—Jerry Bagel, MD

Role of a 2-Compound Ointment in the Treatment Armamentarium for Psoriasis Vulgaris

A pooled analysis of the efficacy of the 2-compound ointment in 2,661 patients with mild, moderate, or severe disease indicated that the drug can be used as initial therapy for most patients (**Figure 11**).[17] Consistent with the results of this and other trials, the roundtable participants stated that they use the 2-compound ointment as first-line therapy for all psoriasis patients amenable to topical therapy, regardless of disease severity.

Jerry Bagel, MD: For me, the 2-compound ointment is first-line topical treatment for psoriasis. Patients need to prove to me that it will not work before I try something else.

Mark Lebwohl, MD: I use the drug as first-line therapy, too. I'll also use it when other topicals are not working well enough, in conjunction with systemic therapies to minimize doses of systemic drugs, and in refractory areas in patients receiving phototherapy.

"For me, the 2-compound ointment is first-line topical treatment for psoriasis. Patients need to prove to me that it will not work before I try something else."

—Jerry Bagel, MD

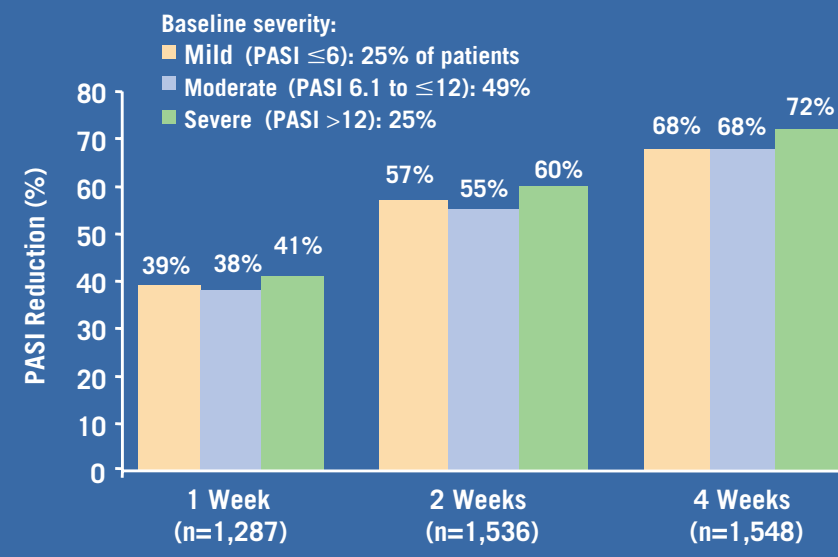
Linda Stein Gold, MD: Since the introduction of the 2-compound ointment, I have used it in a wide variety of psoriasis patients. I find that it works well in patients with localized disease and in patients with more severe disease who have resistant lesions remaining after phototherapy or systemic therapy. I feel that the 2-compound ointment is appropriate for psoriasis patients with all levels of disease severity. It works as monotherapy for localized disease. For patients with more extensive disease, it works well with combination therapy either with systemic agents or when applied after phototherapy.

Craig Leonardi, MD: I agree–the 2-compound ointment is a first-line choice for patients with mild psoriasis, as well as those with most forms of moderate disease. It is a good adjuvant when used in combination with systemic therapies for patients with more severe disease. So, the 2-compound ointment is appropriate therapy for patients with mild, moderate, or severe disease.

"Since the introduction of the 2-compound ointment, I have used it in a wide variety of psoriasis patients… I feel that the 2-compound ointment is appropriate for psoriasis patients with all levels of disease severity."

—Linda Stein Gold, MD

FIGURE 11. The 2-Compound Ointment Has Efficacy Across All Degrees of Disease Severity*



*1,548 patients pooled from five trials; 2-compound ointment was used daily.
PASI = Psoriasis Area and Severity Index.

Source: Menter A, Ganslandt C. Comparative efficacy of calcipotriene/betamethasone dipropionate combination product after 1, 2, and 4 weeks of treatment of mild, moderate, and severe psoriasis. In: 64th Annual Meeting of the American Academy of Dermatology; March 3–7, 2006; San Francisco, CA. *J Am Acad Dermatol*. 2006;54(3 suppl). AB215.

Conclusions

As the roundtable concluded, the participants arrived at several consensus

points regarding the safety, efficacy, and practical considerations of the 2-compound ointment based on trial data and clinical experience (**Table 2**). ■

"I cannot think of a single reason not to use the 2-compound ointment as initial therapy for patients with psoriasis."
—Mark Lebwohl, MD

PANEL CONSENSUS: Role of the 2-Compound Ointment in the Treatment Armamentarium

- The quick onset of action and the convenience of once-daily dosing make the 2-compound ointment ideal for initial therapy for all degrees of psoriasis severity.
- The demonstrated efficacy and safety also support the use of the 2-compound ointment for intermittent maintenance treatment.
- Most patients with psoriasis have mild to moderate disease; the 2-compound ointment is an ideal choice in this population.
- The 2-compound ointment can also be used as monotherapy for carefully selected patients with more severe disease.
- For selected patients with extensive disease, the 2-compound ointment has been used as adjunctive treatment in combination with phototherapy, systemic therapy, or biologic therapy.

TABLE 2. Summary of the Benefits of the 2-Compound Ointment

Advantages of a 2-Compound Ointment vs Superpotent Topical Steroids and Calcipotriene

	2-Compound Ointment	Superpotent Topical Steroids	Calcipotriene
Efficacy			
Reduces cell proliferation	✓	✓	✓
Improves cell differentiation	✓		✓
Reduces inflammation	✓	✓	
Improvement observed in 1 week	✓	✓	
Safety			
Evaluated for long-term safety (52 weeks)	✓		✓
Low incidence of skin atrophy and HPA-axis suppression reported over 52 weeks of use	✓		✓
Convenience			
Replaces the need for sequential/ combination topical therapy	✓		
Only once-daily application needed	✓		
Single co-pay	✓	✓	✓

HPA = hypothalamic-pituitary-adrenal.

PANEL CONSENSUS: The Role of a Novel 2-Compound Ointment as First-Line Therapy

- Replaces many conventional topical treatments
  - Simple and effective treatment regimen
  - Convenient once-daily dosing
  - Improves patient compliance
- Acts quickly and effectively
  - Multiple mechanisms of action
  - Consistent positive results in clinical trials
  - Effective for patients with a range of disease severity
  - Useful for quick clearance and maintenance therapy
- Results in a low incidence of adverse events
  - Effective treatment with a less potent steroid
  - Low incidence of cutaneous irritation, skin atrophy, and adrenal suppression
  - Proven safe for intermittent maintenance therapy in trials up to 52 weeks
- Can play a role in treating all psoriasis patients
  - Initial therapy: all patients
  - Monotherapy: patients with mild to moderate psoriasis
  - Topical adjunct: patients with severe and/or extensive disease
  - Intermittent maintenance therapy: as needed

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Important Safety Information About Taclonex®

- Taclonex® Ointment is indicated for the topical treatment of psoriasis vulgaris in adults 18 years of age and above for up to 4 weeks.
- FOR EXTERNAL USE ONLY – Should not be applied to the face, axillae, or groin.
- Taclonex® Ointment should not be used in patients with hypersensitivity to any of its components; known or suspected disorders of calcium metabolism; or erythrodermic, exfoliative, or pustular psoriasis.
- Systemic absorption of products containing topical corticosteroids, including Taclonex® Ointment, has produced reversible hypothalamic-pituitary-adrenal (HPA)-axis suppression.
- In clinical trials, the most frequent adverse events were pruritus, scaly rash, and worsening of psoriasis.
- Please see Full Prescribing Information for Taclonex® available from your sales representative or at www.taclonex.com.

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