Clindamycin Phosphate 1.2% and Benzoyl Peroxide 2.5% Gel for the Treatment of Moderate-to-severe Acne

An Update

MICHAEL H. GOLD, MD
Gold Skin Care Center and Tennessee Clinical Research Center, Nashville, Tennessee

ABSTRACT

The use of fixed-combination products in acne is commonplace. Clindamycin and benzoyl peroxide are often used in combination, but benzoyl peroxide can cause irritation and dryness, sometimes limiting use. The true bothersome nature of this concentration-dependent tolerability has only recently been elucidated and is significant. An optimized formulation of clindamycin-benzoyl peroxide containing 2.5% benzoyl peroxide has been shown to be highly effective and well-tolerated when used to treat moderate-to-severe acne. A meta-analysis has shown clindamycin phosphate 1.2%–benzoyl peroxide 2.5% gel to be as effective as combinations containing 5% benzoyl peroxide, with possibly greater efficacy in treating noninflammatory lesions. Efficacy in moderate-to-severe and adolescent subpopulations has also been highlighted. Clinical objective assessments, such as lesion counts and physician grading classifications, alone do not adequately capture the impact of acne severity from a patient's perspective. Clindamycin phosphate 1.2%–benzoyl peroxide 2.5% has shown a high level of patient satisfaction and significant improvement in all four acne quality of life domains. This review brings together some of the most recent work on clindamycin phosphate 1.2%–benzoyl peroxide 2.5% gel from one of the most extensive clinical programs ever in moderate-to-severe acne.
(*J Clin Aesthet Dermatol.* 2012;5(1):30–35.)

Fixed-combination products containing clindamycin and benzoyl peroxide (BPO) are widely used in the treatment of acne vulgaris.[1–2] Clindamycin improves acne by reducing the levels of *Propioibacterium acnes* and decreasing inflammation.[3] Products containing BPO are rapidly bactericidal and reduce the development of antibiotic-resistant bacteria.[4] However, a potential limitation of BPO is concentration-dependent dryness and irritation that may impact patient compliance and limit product use.[5] How much patients are bothered by these side effects and what they do to manage the problem has only recently been well-characterized.[6] In an Internet survey of subjects, 15 to 40 years of age, who had used a clindamycin–5% BPO fixed combination product in the last six months, some degree of dryness and irritation occurred in nearly all of the subjects.[6] These side effects were bothersome in the majority of subjects (Table 1), with a third (34%) reporting severe dry skin. Self-adjusted treatment was commonplace; either switching products (in 16% of cases), reducing use (32%), or even stopping medication altogether (10%). These side effects can have an important impact on the dermatologist's office. For example, more than 30 percent of subjects reported calling the physician's office as a result of flaky, dry, or irritated skin; confidence in their physician was affected; and some (11%) said they would be less likely to see the doctor in the future for other skin issues because of side effects. Given that adherence to topical therapy is poor, particularly in teenage acne patients, and no one wants "call backs," it is important to avoid or better manage side effects that reduce adherence. The selection of less irritating

DISCLOSURE: Dr. Gold has served as a consultant and investigator for Coria, Aesthera, Alma Lasers, Dusa, Hoya ConBio, Lumenis, Neocutis, Sciton, and Steifel. He has also served as a consultant for Aerolase and an investigator for Cynosure and has received honoraria or grant support.
ADDRESS CORRESPONDENCE TO: Michael H. Gold, MD, Tennessee Clinical Research Center, 2000 Richard Jones Road, Suite 220, Nashville, TN 37215; E-mail: goldskin@goldskincare.com

TABLE 1. Degree of bother from local adverse events

DEGREE OF BOTHER	DRY SKIN	REDNESS	FLAKY, PEELING SKIN	ITCHY SKIN	IRRITATED SKIN
None	7%	14%	10%	10%	12%
Mild (1–3)	26%	30%	29%	32%	26%
Moderate (4–7)	34%	36%	34%	34%	42%
Severe (8–10)	34%	20%	27%	22%	22%

Patients were asked to rate how bothersome each of those side effects were (or are) while using BenzaClin® or Duac® (1 meaning the effects are not at all bothersome and 10 meaning they are extremely bothersome). Scores are grouped into mild (1–3), moderate (4–7), and sever (8–10).

treatments or treatment regimens aimed at minimizing side effects is a desirable option.[6]

One option was to formulate a clindamycin–BPO fixed combination with a lower concentration of BPO. Even before the patient survey was carried out, a significantly greater frequency and severity of burning, erythema, and peeling had been reported in patients who used topical formulations containing 10% BPO compared with those who used a 2.5% BPO.[7] More recently, fixed combination products containing 5% BPO tested in a cumulative irritation study had been shown to be moderately irritating.[5] Whilst advances in formulation technology, such as removing surfactants and avoiding preservatives, alcohol, or parabens (all known potential irritants), allowed for these irritation levels to be reduced, it was only through using lower concentrations of BPO (2.5%) that significant reductions were achieved.[8]

CLINICAL EXPERIENCE WITH CLINDAMYCIN PHOSPHATE 1.2%–BENZOYL PEROXIDE 2.5% GEL

One of the concerns about reducing the concentration of BPO might be the potential of reduced efficacy. It has been previously reported that 2.5% BPO may be as effective as 5% or 10% BPO in reducing the number of inflammatory lesions of acne.[7] BPO 2.5% also significantly reduced *P. acnes* counts after one week of topical application to the face.[7]

An *in-vitro* percutaneous-penetration study showed that clindamycin phosphate 1.2%–BPO 2.5% achieved comparable skin penetration of BPO to clindamycin–BPO fixed-combinations containing 5% BPO following a single application, although the clinical significance was unknown.[8] The clinical efficacy of clindamycin phosphate 1.2%–BPO 2.5% gel in moderate-to-severe acne has been reported extensively elsewhere.[9–15] After 12 weeks of treatment, there was a 64.1-percent reduction in inflammatory lesion counts and 48.7-percent reduction in noninflammatory lesion counts (Figure 1), compared to 54.0-percent and 40.3-percent median reductions with clindamycin phosphate gel ($p<0.001$), 55.2-percent and 43.8-percent reductions with BPO 2.5% gel ($p<0.001$ and $p=0.001$, respectively), and 34.4-percent and 26.0-percent reductions with vehicle gel ($p<0.001$).[11] In addition, more than one-third of subjects were judged as treatment successes, with at least a two-grade improvement in Evaluator Global Severity Score (EGSS), by the investigators.[10] A recent meta-analysis of 16 randomized, controlled trials (RCTs) in 5,737 subjects sought to compare the efficacy of fixed combinations containing clindamycin–BPO 5% with clindamycin phosphate 1.2%–BPO 2.5% gel.[16] The authors concluded that clindamycin phosphate 1.2%–BPO 2.5% gel was comparable to other topical products containing clindamycin–BPO 5% in reducing lesion counts and may have an advantage over them in treating noninflammatory lesions. Both combination formulations perform better than the single agents alone in treating inflammatory lesions over 10 to 12 weeks and clindamycin phosphate 1.2%–BPO 2.5% gel had a greater absolute reduction in lesion count for both inflammatory and noninflammatory lesions than did clindamycin–BPO 5%.[16] Tolerability and safety endpoints, such as irritation, dryness, erythema, itching, and stinging and burning were not considered. However, with the availability of clindamycin phosphate 1.2%–BPO 2.5% gel, these would be important considerations for any future comparisons.[17]

EFFICACY OF CLINDAMYCIN PHOSPHATE 1.2%–BENZOYL PEROXIDE 2.5% GEL IN SPECIAL POPULATIONS

Currently, two groups of investigators have looked at the efficacy of clindamycin phosphate 1.2%–BPO 2.5% gel in post-hoc analyses of the pivotal clinical studies.

Moderate or severe acne populations. It is probably unique in clinical practice that almost 20 percent of the patients in the pivotal studies with clindamycin phosphate 1.2%–BPO 2.5% gel had severe acne, as this is not a group normally selected for monotherapy.[9] In addition, it is perhaps counter-intuitive that patients with more severe disease would show clinically significant improvement to topical monotherapy, but a comparison study of topical retinoids showed that more severely inflamed subjects had a greater percentage improvement than those with milder disease.[18] It

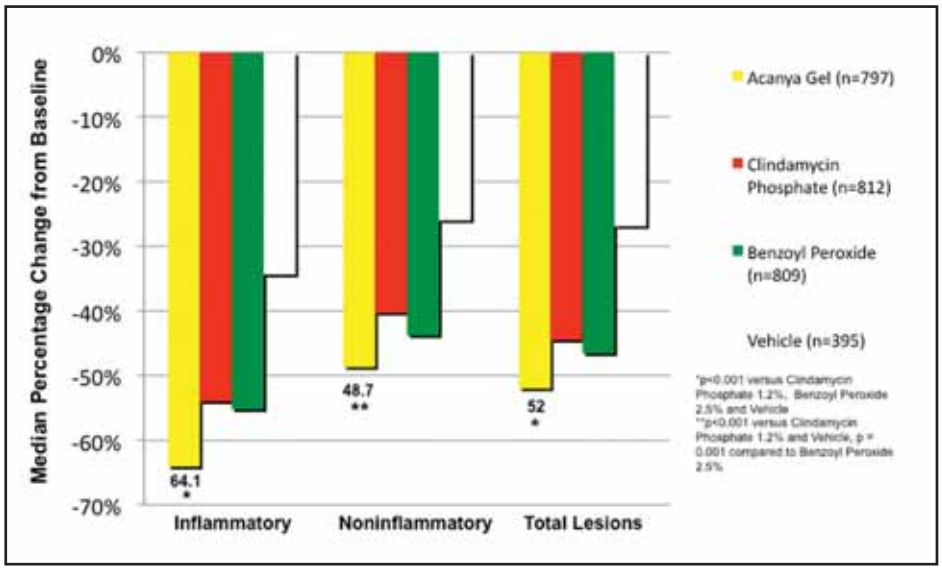

Figure 1. Reduction in inflammatory and noninflammatory lesions

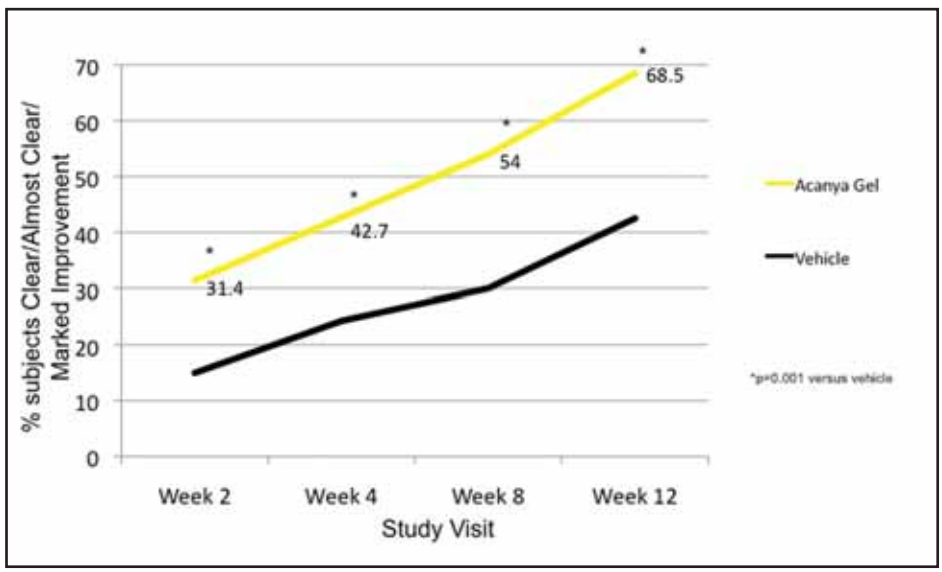

Figure 2. Subject self-assessment—clear/almost clear/marked improvement

is also of interest that 28 percent of subjects in the Internet survey mentioned above reported having severe acne.[6]

More than 45 percent of subjects with severe acne met the criteria for treatment success (a two-grade improvement in the EGSS) at Week 12 with clindamycin phosphate 1.2%–BPO 2.5% gel, suggesting that topical therapy may be more valuable than often assumed in patients with severe acne.[13]

Adolescent acne. Acne may appear in children as young as 8 to 10 years of age, but becomes more common and severe in adolescents. In boys, the prevalence has been estimated at 81 to 95 percent, compared to 79 to 82 percent in girls.[19,20]

Adolescents with acne experience more self-esteem issues, social isolation, depression, and self-consciousness than their peers.[19,21] Despite its psychosocial impact, many adolescents do not seek treatment. In those who do, unrealistic expectations of therapy or poor tolerability can lead to low adherence.[21,22] Effective therapies demonstrating early signs of improvement that are well-tolerated may provide improved adherence and yield significantly improved clinical outcomes.[23] In addition, for adolescent patients, a once-daily treatment is especially preferred for its convenience.[24,25]

In a *post-hoc* analysis of 1,755 adolescent subjects (12 to <18 years of age) with moderate-to-severe acne, a once-daily formulation of clindamycin phosphate 1.2%–BPO 2.5% gel was found to be superior to individual active ingredients and vehicle at Week 12 for all primary and supportive endpoints. More than 31 percent of subjects observed at least "marked" improvements in their acne with clindamycin–BPO 2.5% as early as two weeks after treatment initiation (Figure 2). Satisfaction with clindamycin–BPO 2.5% gel was much greater than with previous therapies and overall subject satisfaction at the end of the study was 81 percent compared to only 27 percent at Baseline ($p<0.001$).[14]

Cutaneous safety (erythema and scaling) and tolerability (itching, burning, and stinging) were evaluated at each study visit on a scale from 0 (none) to 3 (severe). At Baseline and each post-Baseline visit, all scores were less than 1 (mild) and comparable between clindamycin–BPO 2.5% gel and vehicle (Figure 3). Mean scores for burning and stinging with clindamycin–BPO 2.5% gel were 0 (none), 0.1 for itching and erythema, and 0.2 for scaling. No subject in the clindamycin–BPO 2.5% gel group experienced severe local signs or symptoms or discontinued study treatment due to erythema, scaling, itching, burning, or stinging.[14]

It is important that patients start to see improvements within the first two weeks of treatment initiation. Coupled with the simple once-daily dosing regimen, excellent tolerability and high levels of subject satisfaction may encourage treatment adherence and lead to effective acne resolution in this difficult-to-treat population.

PATIENT EXPECTATIONS AND TREATMENT SATISFACTION

In clinical practice, patient expectation of and satisfaction with their acne therapy are important aspects of management. In addition, improved adherence and patient outcomes, including quality of life (QoL) benefits, are correlated with once-daily medications that are perceived by patients to be as safe and effective as treatments with more frequent dosing regimens.[26,27]

The high levels of patient satisfaction with clindamycin phosphate 1.2%–BPO 2.5% gel have been reported previously.[9,11,13] More than 80 percent of subjects were satisfied with their treatment at Week 12 compared to their previous acne therapy prior to the start of the study.[9] It had also been noted that subject self-assessment of acne improvement was higher than that recorded by investigators.[9]

Clinical objective assessments, such as lesion counts and physician grading classifications, alone do not adequately capture the impact of acne severity from a patient's perspective.[28] As a result, assessing the impact of facial acne on health-related quality of life (HRQL) is important to fully characterize the acne burden and the effectiveness of treatment. Also, subject assessment of overall acne severity has been found to correlate higher with patient-reported HRQL than physician-based assessments.[29]

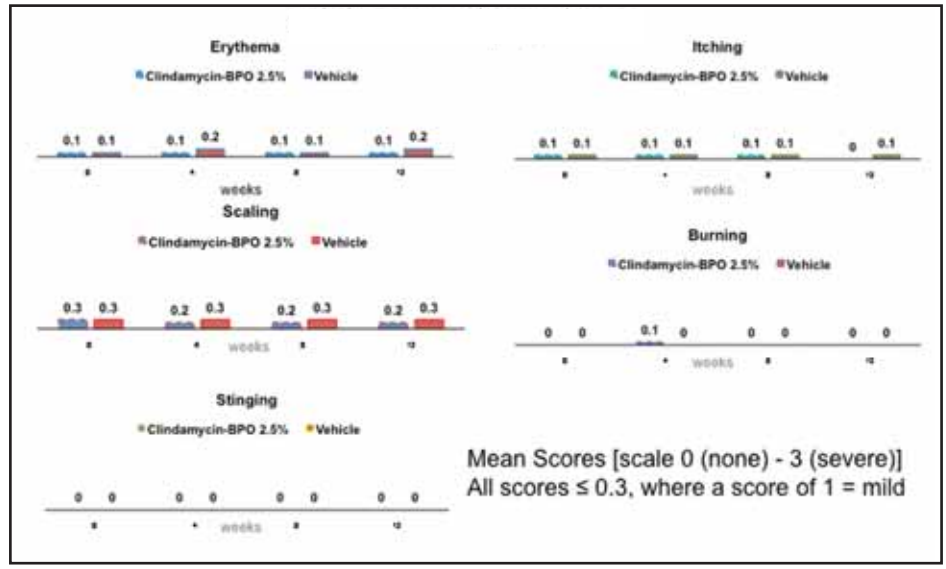

Figure 3. Cutaneous tolerability. Comparison of clindamycin–BPO 2.5% and vehicle in adolescent subpopulation

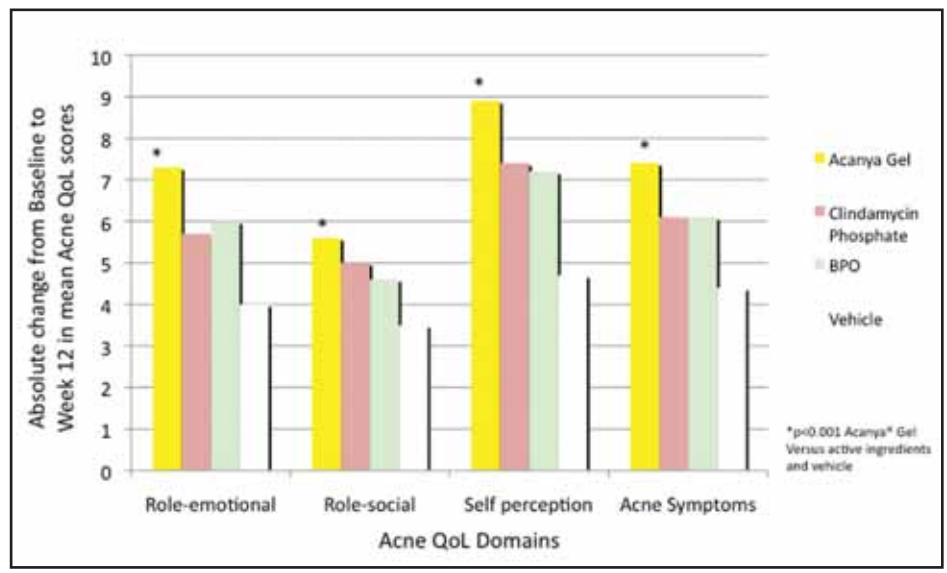

Figure 4. Change in acne QoL domains

Acne treatments can differentially impact HRQL. Consequently, HRQL is an important endpoint in comparative clinical trials complementing the clinical objective assessments of efficacy and tolerability. However, many previous studies of the impact of acne treatments on HRQL have included small numbers of patients[30–35] not fully examined changes in HRQL,[30,36–38] included only patients with mild-to-moderate facial acne,[37,38] or were unblinded observational studies.[38,39]

Improvement in HRQL with clindamycin phosphate 1.2%–BPO 2.5% gel was assessed in the largest ever acne–QoL study. The acne–Qol analyses in this study population demonstrated that treatment with clindamycin phosphate 1.2%–BPO 2.5% gel significantly improved patient perception of their facial acne compared with the individual ingredients and vehicle in moderate-to-severe acne across all four domains of the acne-QoL (Figure 4). The absolute change from Baseline to Week 12 on the acne-QoL for patients treated with clindamycin–BPO 2.5% gel was 7.4 for acne symptoms, 7.3 for role-emotional, 8.9 for self-perception, and 5.6 for role-social. Subjects treated with clindamycin–BPO 2.5% gel had significantly greater improvements in all four acne-QoL domains than patients treated with each individual active ingredient and vehicle ($p<0.001$) consistent with results seen relating to lesion count reduction. At Week 12, the percentage improvement in mean acne-QoL scores with clindamycin–BPO 2.5% gel were 47, 37, 59, and 49 percent for role-emotional, role-social, self-perception, and acne symptoms, respectively. Moreover, the

changes in HRQL observed were also clinically meaningful and a significantly greater proportion of patients receiving clindamycin phosphate 1.2%–BPO 2.5% gel had a clinically meaningful change in HRQL than those in individual active treatment arms.

CONCLUSION

The pivotal clinical data on clindamycin phosphate 1.2%–BPO 2.5% gel was published more than two years ago. At the time, it was the largest study of moderate-to-severe acne and the database continues to provide a wealth of information for us to better understand the management of this very common condition. Talking to sufferers, we are now better aware of how bothersome the concentration-dependent irritation and dryness caused by BPO can be and how patients respond. Thankfully, clindamycin phosphate 1.2%–BPO 2.5% gel has demonstrated excellent tolerability.[8] We now have independent evidence to suggest that efficacy is not compromised by a lower BPO concentration and indeed clindamycin phosphate 1.2%–BPO 2.5% gel may be more efficacious in reducing noninflammatory lesions.[15] *Post-hoc* analyses in two important populations—severe acne, where monotherapy might be considered counter-intuitive, and adolescent acne, where treatment can be particularly challenging—have shown good results with more than 45 percent of severe acne patients being judged as treatment successes, and more than two-thirds of the adolescent patients having at least marked improvement in their acne at 12 weeks. Most importantly, we are able to gain additional insights in relation to patient perception, both in terms of product satisfaction, treatment success, and improved QoL that will be important drivers of our successful management of acne in the future.

ACKNOWLEDGMENT

The authors acknowledge Brian Bulley, MSc, of Inergy Limited for medical writing support. Coria Laboratories, a wholly owned subsidiary of Valeant Pharmaceuticals North America, funded Inergy's activities pertaining to this manuscript.

REFERENCES

1. Ingram JR, Grindlay DJ, Williams HC. Management of acne vulgaris: an evidence-based update. *Clin Exp Dermatol.* 2010;35(4):351–354.
2. Del Rosso JQ. Combination topical therapy in the treatment of acne. *Cutis.* 2006;78(2 Suppl 1):5–12.
3. Webster GF, Jeyden JJ, McGinley KJ, McArthur WP. Suppression of polymorphonuclear leucocyte chemotactic factor production in *Propionibacterium acnes* by subminimal inhibitory concentrations of tetracycline, ampicillin, minocycline, and erythromycin. *Antimicrob Agents Chemother.* 1982;21:770–772.
4. Leyden J. Are 2 combined antimicrobial mechanisms better than 1 for the treatment of acne vulgaris? Clinical and antimicrobial results of a topical combination product containing 1% clindamycin and 5% benzoyl peroxide. Introduction. *Cutis.* 2001;67(2 Suppl):5–7.
5. Dosik JS, Vamvakias G. Comparative irritation potential of two combination acne products: a randomized controlled, subject- and evaluator-blind, comparative study in healthy volunteers. *Am J Clin Dermatol.* 2008;9:313–317.
6. Feldman SR, Chen DM. How patients experience and manage dryness and irritation from acne treatment. *J Drugs Dermatol.* 2011. In press.
7. Mills OH Jr, Kligman AM, Pochi P, Comite H. Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. *Int J Dermatol.* 1986;25:664–667.
8. Bucks D, Sarpotdar P, Yu K, Angel A, Del Rosso J. The development and optimization of a fixed combination of clindamycin and benzoyl peroxide aqueous gel with minimal irritation and enhanced bioavailability. *J Drugs Dermatol.* 2009;8(7) 634–638.
9. Thiboutot D, Zaenglein A, Weiss J, et al. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: Assessment of efficacy and safety in 2813 patients. *J Am Acad Dermatol.* 2008; 59(5):792–800.
10. Bikowski J. Rediscovering topical antimicrobial therapy for acne vulgaris. *Practical Dermatology.* April 2009:55–58.
11. Gold MH. A new, once-daily, optimized, fixed combination of clindamycin phosphate 1.2% and low-concentration benzoyl peroxide 2.5% gel for the treatment of moderate-to-severe acne. *J Clin Aesthet Dermatol.* 2009;2(5):44–48.
12. Cook-Bolden F. Clindamycin phosphate 1.2% and benzoyl peroxide 2.5%: a new, once-daily, fixed combination treatment for moderate to severe acne. *Cosmetic Dermatology.* 2009;22(6):319–322.
13. Webster G, Rich P, Gold MH, et al. Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and low concentration benzoyl peroxide (2.5%) aqueous gel in moderate or severe acne subpopulations. *J Drugs Dermatol.* 2009;8(8):736–743.
14. Novel fixed-combination clindamycin phosphate and low-concentration benzoyl peroxide formulation shows efficacy, tolerability. *Practical Dermatology for Pediatricians.* 2010; July/August: 6–7.
15. Del Rosso JQ. Topical management of acne vulgaris using a combination gel formulation: benzoyl peroxide 2.5%–clindamycin phosphate 1.2% gel. *Expert Review of Dermatology.* 2010;5(6):597–603.
16. Seidler EM, Kimball AB. Meta-analysis of randomized controlled trials using 5% benzoyl peroxide and clindamycin versus 2.5% benzoyl peroxide and clindamycin topical treatments in acne. *J Am Acad Dermatol.* 2011. In press.
17. Seidler EM, Kimball AB. Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne. *J Am Acad Dermatol.* 2010;63:52–62.
18. Leyden JJ, Shalita A, Thiboutot D, Washenik K, Webster G. Topical retinoids in inflammatory acne: a retrospective, investigator-blinded, vehicle-controlled, photographic assessment. *Clin Ther.* 2005;27(2):216–224.
19. Goodman G. Acne—natural history, facts and myths. *Aust Fam Physician.* 2006;35(8):613–616.

20. Goulden V. Guidelines for the management of acne vulgaris in adolescents. *Paediatr Drugs.* 2003;5(5):301–313.
21. Niemeier V, Kupfer J, Gieler U. Acne vulgaris-psychosomatic aspects. *J Dtsch Dermatol Ges.* 2006;4(12):1027–1036.
22. Krakowski AC, Stendardo S, Eichenfield LF. Practical considerations in acne treatment and the clinical impact of topical combination therapy. *Pediatr Dermatol.* 2008; 25(Suppl 1):1–14.
23. Serup J, Lindblad AK, Maroti M, et al. To follow or not to follow dermatological treatment—a review of the literature. *Acta Derm Venereol.* 2006;86(3):193–197.
24. Warner GT, Plosker GL. Clindamycin/benzoyl peroxide gel: a review of its use in the management of acne. *Am J Clin Dermatol.* 2002;3(5):349–360.
25. Berger WE. Once-daily olopatadine ophthalmic solution 0.2% in the treatment of allergic conjunctivitis and rhinoconjunctivitis. *Expert Rev Pharmacoeconomics Outcomes Res.* 2007;7(3):221–226.
26. Hawkins T. Impact of once- and twice-daily dosing regimens on adherence and overall safety. *AIDS Read.* 2004; 14(6):320–322.
27. Richter A, Anton SE, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes. *Clin Ther.* 2003;25(8):2307–2335.
28. Finlay AY. Quality of life measurement in dermatology: a practical guide. *Br J Dermatol.* 1997;136(3):305–314.
29. Ilgen E, Derya A. There is no correlation between acne severity and AQOLS/DLQI scores. *J Dermatol.* 2005; 32(9):705–710.
30. Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. *Br J Dermatol.* 1999;140(4):672–676.
31. Girman CJ, Hartmaier S, Thiboutot D, et al. Evaluating health-related quality of life in patients with facial acne: development of a self-administered questionnaire for clinical trials. *Qual Life Res.* 1996;5(5):481–490.
32. Gupta MA, Johnson AM, Gupta AK. The development of an Acne Quality of Life scale: reliability, validity, and relation to subjective acne severity in mild to moderate acne vulgaris. *Acta Derm Venereol.* 1998;78(6):451–456.
33. Motley RJ, Finlay AY. Practical use of a disability index in the routine management of acne. *Clin Exp Dermatol.* 1992; 17(1):1–3.
34. Klassen AF, Newton JN, Mallon E. Measuring quality of life in people referred for specialist care of acne: comparing generic and disease-specific measures. *J Am Acad Dermatol.* 2000;43(2 Pt 1):229–233.
35. Newton JN, Mallon E, Klassen A, Ryan TJ, Finlay AY. The effectiveness of acne treatment: an assessment by patients of the outcome of therapy. *Br J Dermatol.* 1997;137(4): 563–567.
36. Kellett SC, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. *Br J Dermatol.* 1999;140(2):273–282.
37. Simpson N. Effect of isotretinoin on the quality of life of patients with acne. *Pharmacoeconomics.* 1994;6(2): 108–113.
38. Jones-Caballero M, Chren MM, Soler B, Pedrosa E, Penas PF. Quality of life in mild to moderate acne: relationship to clinical severity and factors influencing change with treatment. *J Eur Acad Dermatol Venereol.* 2007;21(2):219–226.
39. Martin AR, Lookingbill DP, Botek A, et al. Health-related quality of life among patients with facial acne—assessment of a new acne-specific questionnaire. *Clin Exp Dermatol.* 2001;26(5):380–385.