Two randomized, double-blind, controlled trials of 2219 subjects to compare the combination clindamycin/tretinoin hydrogel with each agent alone and vehicle for the treatment of acne vulgaris

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Background: The development of a hydrogel to stabilize and solubilize clindamycin and tretinoin provides a single, once-daily treatment for acne vulgaris.

Objective: Our aim was to compare the efficacy and safety of the combination of clindamycin (1%) and tretinoin (0.025%) with each agent alone and vehicle.

Methods: Two randomized, double-blind, active drug− and vehicle-controlled 12-week studies evaluated inflammatory and noninflammatory lesion counts and the Investigator's Static Global Assessment in 2219 subjects with acne vulgaris.

Results: The combination demonstrated superior efficacy to clindamycin, tretinoin, and vehicle. Combination hydrogel was significantly more effective in reducing inflammatory ($P < .005$), noninflammatory ($P \leq .0004$), and total ($P < .0001$) lesion counts than the other treatments and vehicle. The proportion of subjects with clear or almost clear skin on the Investigator's Static Global Assessment was greater with the combination ($P < .0001$).

Limitations: A majority of subjects (82.6%) had grade 2-3 acne vulgaris at baseline; therefore these overall results may not be representative of the response in the subjects (17.4%) with grade 4-5 acne.

Conclusion: The combination clindamycin/tretinoin hydrogel was well tolerated and significantly more effective than clindamycin, tretinoin, or vehicle for the treatment of acne vulgaris. (J Am Acad Dermatol 2006;54:73-81.)

Acne is a multifactorial disease involving pilosebaceous follicles. Excess sebum production and abnormal desquamation of follicular epithelium provide an environment (microcomedo) in which *Propionibacterium acnes* proliferation occurs with noninflammatory comedones and inflammatory papules, pustules, and nodules as the clinical expression of these areas of pathophysiology. In a recent consensus conference, the combination of a topical retinoid and an antibiotic were recommended for the treatment of acne in a majority of patients.[1,2] Until now these two classes of drugs had to be used separately because they were not readily formulated in one compound. The inconvenience of such a treatment regimen may reduce the chance for an optimal response because of poor compliance,[3-6] particularly in the teenaged population. Recent advances in delivery vehicles now permit the combination of topical tretinoin and clindamycin in one formulation. We describe herein the results from two 12-week randomized, active

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Table I. Investigator's Static Global Assessment Scale

Grade 0	Normal, clear skin with no evidence of acne vulgaris
Grade 1	Skin almost clear: rare noninflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red) requiring no further treatment in the investigator's opinion
Grade 2	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodulocystic lesions)
Grade 3	Noninflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesion
Grade 4	Inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulocystic lesions
Grade 5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules and nodulocystic lesions

drug— and vehicle-controlled clinical trials in which the combination of clindamycin (1%) and tretinoin (0.025%) in the hydrogel (Velac, Connetics Corporation, Palo Alto, Calif) was compared with tretinoin, clindamycin, and the vehicle in 2219 subjects.

METHODS

Study population

A total of 2219 male and female subjects at 37 US sites were enrolled in these two studies. To be included in the studies, subjects had to be 12 years or older with an Investigator's Static Global Assessment (ISGA) score of 2 or higher, 17 to 40 facial inflammatory lesions (papules plus pustules) including nasal lesions, and 20 to 150 facial noninflammatory lesions (open and closed comedones), excluding nasal lesions (Table I). Informed consent documents were signed.

Subjects were excluded if they (1) had any nodulocystic lesions at baseline; (2) had a history or presence of regional enteritis or inflammatory bowel disease and/or similar symptoms, known hypersensitivity or previous allergic reaction to any of the active components of the study medication, and/or current drug or alcohol abuse; (3) had a facial procedure (eg, chemical or laser peel, microdermabrasion) 2 weeks before or during the study, used any investigational therapy, topical antiacne medications and/or systemic corticosteroids 4 weeks before study start and/or systemic retinoids 12 weeks before study start; (4) were pregnant, nursing, and/or using oral contraceptives with a specific antiandrogenic action or any oral contraceptive treatment initiated within 12 weeks before or during the study; and (5) concurrently or concomitantly used photosensitizers, neuromuscular blocking agents, medications reported to exacerbate acne, certain types of facial products, and/or tanning booths or sunbathing. Subjects were excluded for any other condition that in the judgment of the investigator would put the subject at unacceptable risk for participation in the study.

Study design

These two studies were randomized, double-blind, active drug— and vehicle-controlled, multicenter clinical studies of the combination of clindamycin (1%) and tretinoin (0.025%) solubilized in an alcohol-free hydrogel compared with clindamycin (1%) hydrogel, tretinoin (0.025%) hydrogel, and hydrogel alone (vehicle). Subjects were randomized to one of four parallel treatment groups in a 2:2:2:1 ratio (combination:clindamycin:tretinoin:vehicle) following a randomization list generated before enrollment. Each subject was assigned a subject number at enrollment, which defined the study drug assignment. Hydrogel treatments were packaged in blinded containers showing the subject number. The investigator, nurse/coordinator, patient, and Connetics personnel were all blinded as to subject treatment assignments. All treatments were administered once daily in the evening from baseline through week 12. Subjects were evaluated at baseline (week 0/day 1), week 2, week 4, week 8, and week 12.

These two studies were powered on the basis of results of 6 European efficacy and safety studies comparing combination hydrogel to that of clindamycin and tretinoin.[7-10] Allowing for a 20% rate of attrition, it was estimated that 847 subjects (242 in each active group and 121 in the vehicle group) would be required to establish superiority of the combination hydrogel to clindamycin hydrogel, tretinoin hydrogel, and the vehicle at the .05 significance level, with at least 80% power to detect a 10% difference in the reduction of total lesions. For the ISGA comparison, this sample size was calculated to be sufficient to establish superiority of the combination to the comparators at the .05 significance level with 80% power. The power of the pooled analysis including 2219 subjects was in excess of 90%. An institutional review board at each site approved the protocol used at that site.