

# The Efficacy and Safety of Adapalene Gel 0.3% in the Treatment of Acne Vulgaris: A Randomized, Multicenter, Investigator-Blinded, Controlled Comparison Study Versus Adapalene Gel 0.1% and Vehicle

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*A randomized, multicenter, investigator-blinded, active- and vehicle-controlled study was conducted to evaluate the efficacy and safety of adapalene gel 0.3% versus adapalene gel 0.1% and the corresponding gel vehicle. Subjects were assigned randomly to receive either adapalene gel 0.3%, adapalene gel 0.1%, or vehicle once daily for 12 weeks. A total of 214 subjects with moderate to moderately severe acne vulgaris were enrolled, and 85% of subjects*

*completed the study. Adapalene gel 0.3% was significantly superior to adapalene gel 0.1% in total and noninflammatory lesion counts and in global severity score ( $P < .05$  for all). A concentration-dependent increase in clinical benefit for all efficacy assessments was observed. As expected, there were also statistically significant differences in all efficacy parameters in the adapalene gel 0.3% group relative to the vehicle group ( $P < .001$  for all). Treatment-related adverse events were mostly mild-to-moderate and similar between active groups. The results of this study show that adapalene gel 0.3% was superior to adapalene gel 0.1% and vehicle in the treatment of moderate to moderately severe acne while retaining a similar safety and tolerability profile to adapalene 0.1% gel.*

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Drs. Pariser and Jones report no conflict of interest. Dr. Thiboutot is on the advisory board and in the speakers program for Galderma Laboratories, Inc. Dr. Clark is on the advisory board for Galderma Laboratories, Inc. Drs. Liu and Graeber are employees of Galderma R&D, Inc, and Dr. Graeber holds a patent for a product mentioned in this article. This study was funded by Galderma R&D, Inc. The investigating authors received honoraria for this research project.

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Adapalene is a naphthoic-acid derivative developed for the topical treatment of acne vulgaris. Adapalene has potent, receptor-selective retinoid properties, including modulation of cellular differentiation and stabilization of abnormal desquamation.<sup>1-3</sup> Additionally, the anti-inflammatory properties of adapalene have been demonstrated in both in vitro and in vivo research, as well as in clinical studies.<sup>3-5</sup>

The efficacy and safety of adapalene in the treatment of acne vulgaris has been extensively

studied. Clinical data from studies with various formulations of adapalene 0.1% concentration have demonstrated a fast onset of action and equivalent efficacy to tretinoin.<sup>5-9</sup> In addition, adapalene has been shown to provide an additional clinical benefit when used in combination therapy with oral and topical antibiotics in the treatment of inflammatory acne.<sup>10-11</sup> Adapalene is safe and well tolerated,<sup>12</sup> demonstrating a more favorable tolerability profile than other topical retinoids, including all tazarotene and tretinoin formulations.<sup>5-9,13-18</sup>

Adapalene is available in gel, cream, solution, and pledget formulations for the topical treatment of acne vulgaris but is currently only available in a single concentration, 0.1%. In an effort to expand the treatment armamentarium available for the management of acne and to allow increased flexibility to physicians prescribing adapalene, a 0.3% formulation of adapalene gel was developed. The aim of this dose-assessment study was to evaluate the efficacy of adapalene gel 0.3% versus the currently available adapalene gel 0.1% and the corresponding vehicle. This study also compares the local and systemic safety profile of adapalene gel 0.3% versus adapalene gel 0.1%.

## Methods

This study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with good clinical practices and local regulatory requirements. This study and all appropriate amendments were reviewed and approved by an institutional review board. All subjects provided written informed consent before entering the study.

**Study Design and Population**—This was a randomized, investigator-blinded, balanced parallel-group, active- and vehicle-controlled study conducted at 11 centers in the United States. Subjects were 12 to 40 years old with moderate to moderately severe acne vulgaris and randomized to receive either adapalene gel 0.3%, adapalene gel 0.1%, or vehicle in a 1:1:1 ratio. Subjects were required to have a minimum of 20 inflammatory facial lesions (not >2 nodules/cysts), 20 noninflammatory facial lesions, and a global facial severity grade from 4 to 10 according to the Leeds Revised Acne Grading System.<sup>19</sup> Washout periods for certain topical and systemic treatments were required. Medication was dispensed by a third party to protect blinding. Subjects applied the study treatment to affected areas once daily for 12 weeks. Visits occurred at baseline and at weeks 1, 2, 4, 8, and 12. Negative urine pregnancy test results were required at screening and at the

final study visit for all female subjects of childbearing potential. Subjects could withdraw from the study at anytime.

**Efficacy and Safety Assessments**—Efficacy evaluations consisted of lesion counts (total, inflammatory, and noninflammatory) and global severity grades based on the Leeds Revised Acne Grading System. Lesion counts and global severity grades were assessed on the face only. The same evaluator was to perform all assessments at all visits for a given subject.

Safety was assessed by evaluating adverse events (AEs). In addition, hematology, serum chemistries, urinalysis, and plasma adapalene levels were obtained at 5 selected sites. Blood and urine samples for laboratory analysis were obtained at screening and at the final study visit. Blood tests for adapalene analysis was obtained at weeks 2, 8 and 12.

**Statistical Analyses**—All data analyses were carried out according to a preestablished analysis plan. A sample size of 86 subjects per group was deemed necessary to detect statistically significant differences between the adapalene gel and vehicle groups based on the use of a 2-tailed test with  $\alpha=0.5$  and a power of 80%, an assumption of an average difference between adapalene 0.3% gel and vehicle of 0.75 units and a standard deviation of 1.6 (based on change in transformed lesion counts), and a dropout rate of 15%.

Demographic variables were tested for comparability among the 3 treatment groups. Three study populations were analyzed. The safety population was defined as all subjects randomized and treated at least once. The intent-to-treat (ITT) population included all randomized subjects who were dispensed the study medication. The per-protocol (PP) population included all randomized subjects without any major protocol deviations.

The objective was to show superior efficacy of the adapalene gel 0.3% versus the vehicle and to assess the magnitude of treatment differences between the 0.3% and 0.1% concentrations. Efficacy analyses were conducted for both the ITT and PP populations. Lesion counts were normalized for analysis by using the square root transformation to meet assumption for homogeneity of variance. An analysis of covariance model with terms for treatment, center, and baseline as covariate was used to analyze transformed lesion counts and global facial severity grades. All *P* values for lesion counts were based on the transformed lesion reduction. The Cochran-Mantel-Haenszel test, or the log-rank test, using RIDIT (Relative to an Identified Distribution)-transformed score was used to analyze global assessment of acne, stratified

## Subject Demographics and Baseline Characteristics (Intent-to-Treat Population)

	Adapalene Gel 0.3% (n=70)	Adapalene Gel 0.1% (n=70)	Gel Vehicle (n=74)	Total (N=214)	P value*
Gender, n (%)					
Male	38 (54.3)	43 (61.4)	45 (60.8)	126 (58.9)	.643
Female	32 (45.7)	27 (38.6)	29 (39.2)	88 (41.1)	
Race, n (%)					
White	48 (68.6)	46 (65.7)	53 (71.6)	147 (68.7)	.844
Black	7 (10.0)	8 (11.4)	8 (10.8)	23 (10.7)	
Asian	0	1 (1.4)	0	1 (0.5)	
Hispanic	15 (21.4)	14 (20.0)	12 (16.2)	41 (19.2)	
Other	0	1 (1.4)	1 (1.4)	2 (0.9)	
Age, y					
Mean±SD	17.8±6.02	16.5±4.51	17.6±4.55	17.3±5.07	.241
Median (range)	15.5 (12–40)	15.0 (12–45)	17.0 (12–35)	16.0 (12–45)	
Age distribution, n (%)					
12–17 y	47 (67.1)	55 (78.6)	45 (60.8)	147 (68.7)	.063
18–40 y	23 (32.9)	15 (21.4)	29 (39.2)	67 (31.3)	
Mean lesion counts <sup>†</sup>					
Inflammatory	32.7	31.1	29.6		.31
Noninflammatory	47.0	49.4	41.7		.085
Total	79.8	80.6	71.5		.11

\*P values for categorical variables were based on the Cochran-Mantel-Haenszel general association statistic, adjusted for center. P values for continuous variables were based on a 2-way analysis of variance model with terms for treatment and center.

<sup>†</sup>Lesion counts were transformed using the square root transformation before analysis.

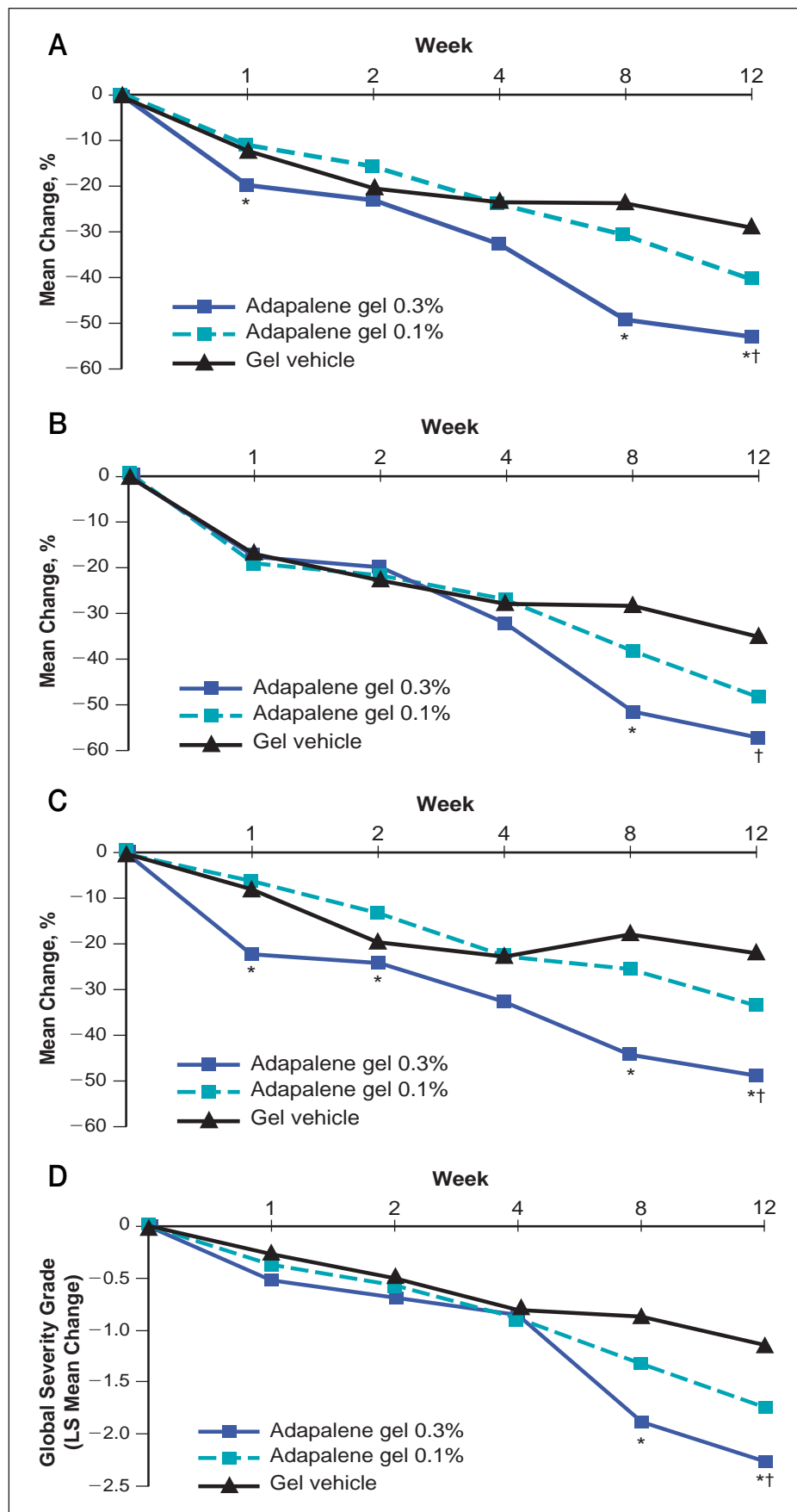
by center. All tests were 2 sided and used a 0.05 significance level.

### Results

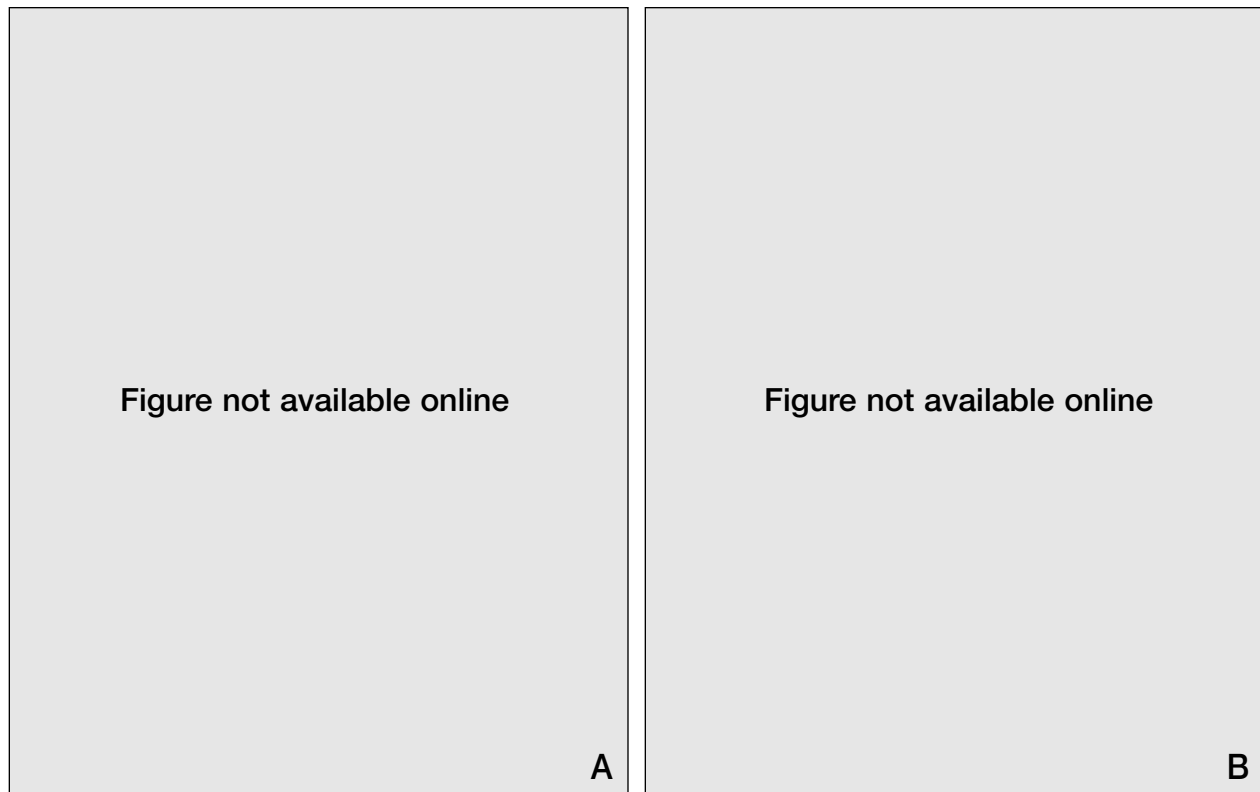
**Subject Disposition and Baseline Characteristics**—A total of 329 subjects were screened for participation in this study, and 214 subjects (mean age, 17.3±5.07 years) were randomized and included in the ITT population: 70 received adapalene gel 0.3%, 70 received adapalene gel 0.1%, and 74 received vehicle. Subject disposition was similar among the treatment groups. The safety population included all ITT subjects. The PP population consisted of 190 subjects (89%). Overall, 85% of subjects completed the study. Discontinuation rates were 21% (15) in the adapalene gel 0.3% treatment group, 7% (5) in the adapalene gel 0.1%

group, and 16% (12) in the vehicle group. Subject request was the most frequent reason for discontinuation (adapalene gel 0.3%, 7 [10%]; adapalene gel 0.1%, 2 [3%]; and vehicle, 6 [8%]). AEs accounted for 4 (6%), 2 (3%), and 0 discontinuations in the adapalene gel 0.3%, 0.1%, and vehicle groups, respectively. The treatment groups were comparable in demographics and baseline characteristics (Table).

**Efficacy Evaluation**—Mean percentage changes in lesion counts (total, inflammatory, and noninflammatory) and mean changes in global assessment of acne severity from baseline at weeks 1, 2, 4, 8, and 12 are shown in Figure 1. The adapalene gel 0.3% group consistently demonstrated superior reductions for all efficacy assessments versus the adapalene gel 0.1% group. At the end of the study,



**Figure 1.** Percentage reduction in total (A), inflammatory (B), and noninflammatory (C) lesion counts (based on the transformed score of lesion counts), as well as the least squares (LS) mean change in global severity grade (D)(based on the Leeds Revised Acne Grading System). Asterisk indicates  $P < .05$  for adapalene gel 0.3% vs adapalene gel 0.1%; dagger,  $P < .001$  for adapalene gel 0.3% vs vehicle.



**Figure 2.** Facial lesions before (A) and after (B) 12 weeks of treatment with adapalene gel 0.3%.

statistically significant differences were observed between adapalene gel 0.3% and 0.1% in total lesion counts (mean percentage reductions, 53.2% vs 40.6%;  $P=.014$ ) and in noninflammatory lesion counts (49.0% vs 34.0%;  $P=.024$ ). Significant differences between adapalene gel 0.3% and 0.1% were observed as early as week 1 for total and noninflammatory lesions ( $P<.05$ ). For inflammatory lesions, the differences between adapalene gel 0.3% and adapalene gel 0.1% were significant at week 8 (51.7% vs 38.6%;  $P=.015$ ). In addition, significant differences were observed in the mean reduction in global severity (least square mean change,  $-2.26$  vs  $-1.74$ ;  $P=.021$ ) and in the percentage of subjects achieving 2 or more grades in global severity change between adapalene gel 0.3% and 0.1% (51.8% vs 30.8%;  $P=.028$ ) after 12 weeks of treatment.

As expected, there were significant reductions in total lesion counts (mean percentage reductions, 53.2% vs 28.5%;  $P<.001$ ), inflammatory lesion counts (57.5% vs 35.5%;  $P<.001$ ), noninflammatory lesion counts (49.0% vs 21.9%;  $P<.001$ ), and global severity assessment (least square mean change,  $-2.26$  vs  $-1.14$ ;  $P<.001$ ) in the adapalene gel 0.3% group versus the vehicle group at week 12

(Figure 1). Statistically significant reductions in the adapalene gel 0.3% group versus the vehicle were observed as early as week 1 in total lesion and noninflammatory lesion counts and week 8 in inflammatory lesion counts and global severity grades. Statistically significant differences were observed in the mean reduction in global severity grade (least square mean change:  $-2.26$  vs  $-1.14$ ;  $P<.001$ ) and in the number of subjects achieving 2 or more grades in global severity change between adapalene gel 0.3% and vehicle (51.8% vs 9.7%;  $P<.0001$ ) after 12 weeks of treatment. Results in the PP population were similar.

Total lesion counts were summarized and analyzed by subgroup for gender, age group (<18 vs 18–40 years), and race (Caucasian vs non-Caucasian). At end point, the differences between adapalene gel 0.3% and vehicle were significant for all subgroups and numerically greater reductions in all subgroups were observed for adapalene gel 0.3% versus adapalene gel 0.1% ( $P<.05$  for all). Figure 2 shows the effect of adapalene gel 0.3% on facial lesions in one subject after 12 weeks of treatment.

**Safety Evaluation**—The number of subjects reporting 1 or more AEs was similar in all groups (36 subjects [51%] in the adapalene gel 0.3% group,

38 [54%] in the adapalene gel 0.1% group, and 30 [41%] in the vehicle group). Treatment-related AEs occurred in 28 subjects (40%) receiving adapalene gel 0.3%, 26 (37%) receiving adapalene gel 0.1%, and 5 (7%) receiving vehicle. Dry skin was the most commonly reported AE (23% [16] in the adapalene gel 0.3% group and 19% [13] in the adapalene gel 0.1% group). Erythema was more prevalent in the adapalene gel 0.3% group than in the adapalene gel 0.1% group (11% [8] and 4% [3], respectively; all erythema was mild or moderate). Irritant dermatitis occurred in 3% (2) of subjects using adapalene gel 0.3% and in 10% (7) of those using adapalene gel 0.1%. Treatment-related AEs were all dermatologic and mostly mild to moderate in severity. No serious AEs were reported.

A total of 6 subjects discontinued because of AEs, 5 of which were treatment-related. In the adapalene gel 0.3% group, 3 subjects (4.3%) discontinued treatment because of a treatment-related AE. In the adapalene gel 0.1% group, 2 subjects (2.9%) discontinued treatment because of a treatment-related AE. All but 1 of the events leading to discontinuation were mild or moderate dermatologic events.

No clinically significant shifts in laboratory parameters were observed, and no quantifiable adapalene plasma levels were detected.

### Comment

This randomized, multicenter, investigator-blinded, dose-assessment study was designed to evaluate the efficacy and safety of adapalene gel 0.3% compared with the currently available adapalene gel 0.1% and the corresponding vehicle in the treatment of moderate to moderately severe inflammatory acne vulgaris. Results indicate that adapalene gel 0.3% consistently provided a dose-dependent clinical benefit relative to the 0.1% formulation and vehicle for all efficacy assessments. Adapalene gel 0.3% provides a fast onset of action, as evidenced by the statistically significant differences in total lesion counts were observed in the adapalene gel 0.3% group as early as week 1 compared with vehicle ( $P < .05$ ).

This is the first clinical study detailing the efficacy of adapalene gel 0.3%. However, the results are consistent with previously published studies demonstrating the efficacy of various formulations of adapalene 0.1% in the treatment of acne vulgaris.<sup>6-9</sup> The results of this study also support a subsequent larger study (653 subjects) with a similar design, in which adapalene gel 0.3% was shown to have a statistically more effective success rate and a greater reduction in total and inflammatory lesion counts relative to the 0.1% formulation ( $P < .05$  for all).<sup>20</sup>

Adapalene gel 0.3% was found to be safe and well tolerated in this study. The incidence of treatment-related AEs in the adapalene gel 0.3% group was similar to that of the adapalene gel 0.1% group (and consistent with those commonly observed with topical retinoids) and were mostly mild to moderate in severity. The results of this study support published evidence of the safety and tolerability of adapalene.<sup>5,6,13-18</sup>

In summary, adapalene gel 0.3% was significantly superior to the vehicle in reducing global severity score and total, inflammatory, and noninflammatory lesion counts ( $P < .05$ ). Furthermore, adapalene gel 0.3% was consistently more effective than adapalene gel 0.1% in all efficacy assessments, providing a concentration-dependent increase in clinical benefit. Adapalene gel 0.3% was well tolerated and safe, with an overall safety profile similar to the currently marketed adapalene gel 0.1%. The availability of a higher concentration of adapalene gel will provide more options for physicians to tailor the management of acne vulgaris in accordance with the presentation of the disease.

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### REFERENCES

1. Gollnick H, Schramm M. Topical drug treatment in acne. *Dermatology*. 1998;196:119-125.
2. Brogden RN, Goa KL. Adapalene: a review of its pharmacological properties and clinical potential in the management of mild to moderate acne. *Drugs*. 1997;53:511-519.
3. Michel S, Jomard A, Demarchez M. Pharmacology of adapalene. *Br J Dermatol*. 1998;139(suppl 52):3-7.
4. Vega B, Jomard A, Michel S. Regulation of human monocyte toll-like receptor 2 (TLR2) expression by adapalene [abstract]. *J Eur Acad Dermatol Venereol*. 2002;16(suppl 1):123-124.
5. Cunliffe WJ, Caputo R, Dreno B, et al. Clinical efficacy and safety comparison of adapalene gel and tretinoin gel

- in the treatment of acne vulgaris: Europe and US multicenter trials. *J Am Acad Dermatol.* 1997;36:S126-S134.
6. Shalita A, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol.* 1996;34:482-485.
  7. Grosshans E, Marks R, Mascaro JM, et al. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. *Br J Dermatol.* 1998;139:26-33.
  8. Thiboutot D, Gold MH, Jarratt MT, et al. Randomized controlled trial of the tolerability, safety, and efficacy of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. *Cutis.* 2001;68(suppl 4):10-19.
  9. Cunliffe WJ, Poncet M, Loesche C, et al. A comparison of the efficacy and tolerability of adapalene 0.1% gel versus tretinoin 0.025% gel in patients with acne vulgaris: a meta-analysis of five randomized trials. *Br J Dermatol.* 1998;139:48-56.
  10. Wolf JE Jr, Kaplan D, Kraus SJ, et al. Efficacy and tolerability of combined topical treatment of acne vulgaris with adapalene and clindamycin: a multicenter, randomized, investigator-blinded study. *J Am Acad Dermatol.* 2003;49:S211-S217.
  11. Cunliffe WJ, Meynadier J, Alirezai M, et al. Is combined oral and topical therapy better than oral therapy alone in patients with moderate to moderately severe acne vulgaris? a comparison of the efficacy and safety of lymecycline plus adapalene gel 0.1%, versus lymecycline plus gel vehicle. *J Am Acad Dermatol.* 2003;49(suppl 3):S218-S226.
  12. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(suppl 1):S1-S37.
  13. Dosik JS, Homer K, Arsonnaud S. Cumulative irritation potential of adapalene 0.1% cream and gel compared with tazarotene cream 0.05% and 0.1%. *Cutis.* 2005;75:289-293.
  14. Greenspan A, Loesche C, Vendetti N, et al. Cumulative irritation comparison of adapalene gel and solution with 2 tazarotene gels and 3 tretinoin formulations. *Cutis.* 2003;72:76-81.
  15. Brand B, Gilbert R, Baker MD, et al. Cumulative irritancy comparison of adapalene gel 0.1% versus other retinoid products when applied in combination with topical antimicrobial agents. *J Am Acad Dermatol.* 2003;49(suppl 3):S227-S232.
  16. Dunlap FE, Mills OH, Tuley MR, et al. Adapalene 0.1% gel for the treatment of acne vulgaris: its superiority compared to tretinoin 0.025% cream in skin tolerance and patient preference. *Br J Dermatol.* 1998;139:17-22.
  17. Caron D, Sorba V, Kerrouche N, et al. Split-face comparison of adapalene 0.1% gel and tretinoin 0.025% gel in acne patients. *J Am Acad Dermatol.* 1997;36(suppl 6, pt 2):S110-S112.
  18. Egan N, Loesche MC, Baker MM. Randomized, controlled, bilateral (split-face) comparison trial of the tolerability and patient preference of adapalene gel 0.1% and tretinoin microsphere gel 0.1% for the treatment of acne vulgaris. *Cutis.* 2001;68(suppl 4):20-24.
  19. O'Brien SC, Lewis JB, Cunliffe WJ. The Leeds Revised Acne Grading System. *J Dermatol Treat.* 1998;9:215-220.
  20. Thiboutot DM, Pariser DM, Egan N, et al. Adapalene gel 0.3% for the treatment of acne vulgaris: a randomized, controlled trial. *J Am Acad Dermatol.* In press.