Clinical Study Synopsis for Public Disclosure

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2 SYNOPSIS

NAME OF COMPANY: Galderma R&D Inc.	***For regulatory use only***	
NAME OF FINISHED MEDICINAL PRODUCT: Adapalene/Benzoyl Peroxide Topical Gel		
NAME OF ACTIVE INGREDIENT(S): adapalene, benzoyl peroxide		

Title of Study:	A Multicenter, Randomized, Double-Blind, Parallel-Group Study to Demonstrate the Efficacy and Safety of Adapalene/Benzoyl Peroxide Topical Gel Compared with Adapalene Topical Gel, 0.1%; Benzoyl Peroxide Topical Gel, 2.5% and Topical Gel Vehicle in Subjects with Acne Vulgaris
Investigator(s):	Multicenter study conducted in the United States, Canada, Germany, Hungary, and Poland.
Study Center(s):	61 investigational sites in the United States, Canada, Germany, Hungary, and Poland
Clinical Phase:	3
Period of Study (years): (date of first enrollment): (date of last subject completed):	 October 24, 2006 October 5, 2007
Publication(s):	Not applicable at time of report.
Study Objective(s):	To demonstrate the superiority in efficacy and assess safety of Adapalene/Benzoyl Peroxide Topical Gel (Adapalene/Benzoyl Peroxide Gel) versus Adapalene Topical Gel, 0.1% (Adapalene Monad); Benzoyl Peroxide Topical Gel, 2.5% (Benzoyl Peroxide Monad) and Topical Gel Vehicle (Gel Vehicle) in the treatment of acne vulgaris for up to 12 weeks.
Methodology:	A multicenter, randomized, double-blind, parallel-group study with 12 weeks of treatment for acne vulgaris. Efficacy and safety evaluations were performed at Screening, Baseline and Weeks 1, 2, 4, 8 and 12. All evaluators were trained and approved.
Number of Subjects (planned and analyzed):	Planned: approximately 1656 subjects; Screened: 1843 subjects; Randomized: 1670 subjects; and Analyzed: 1670 subjects for ITT and Safety populations.
Diagnosis and Inclusion Criteria:	Male and female subjects, of any race, 12 years of age or older, with acne vulgaris with facial involvement. Eligible subjects must have presented with an Investigator's Global Assessment (IGA) score of "3" (Moderate) and have 20 to 50 inflammatory lesions and 30 to 100 noninflammatory lesions on the face (excluding the nose) at Baseline. Subjects with one nodule at Baseline were also included.
Test Product Dosage Form (Batch/formulation number)	Adapalene/Benzoyl Peroxide Gel (044740 / 555.610)
Reference Therapies (Batch/formulation number)	Adapalene Gel, 0.1% (016*06 / 555.613) Benzoyl Peroxide Gel, 2.5% (011*06 / 555.611) Gel Vehicle (014*06 /555.612)
Route of Administration/ Dosage regimen	Topical/One application daily in the evening
Duration of Treatment	12 weeks

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Criteria for Evaluation:	
Efficacy:	Primary Endpoints: Success Rate - defined as the percentage of subjects rated Clear or Almost Clear on the Investigator's Global Assessment (IGA) at Week 12, Last Observation Carried Forward (LOCF), Intent to Treat Population (ITT): Change in Lesion Counts: ■ Change in Inflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT) ■ Change in Noninflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT) Secondary Endpoints: Percent Change in Lesion Counts: ■ Percent Change in Inflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT) ■ Percent Change in Noninflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT) ■ Percent Change in Total Lesion Counts from Baseline to Week 12 (LOCF, ITT) Tertiary Endpoints: ■ Change in IGA from Baseline to Week 12 (LOCF, ITT) ■ Subject's Assessment of Acne at Week 12 (LOCF, ITT)
Safety:	■ Spontaneously reported Adverse Events (AEs) ■ Local Tolerability Assessments (Erythema, Scaling, Dryness and Stinging/Burning) assessed on scales ranging from "0" (None) to "3" (Severe)
Other Endpoints:	■ Change in Dermatology Life Quality Index and Children's Dermatology Life Quality Index (DLQI/C-DLQI) from Baseline to Week 12/Early Termination ■ Appreciation Questionnaire at Week 12
Principal Statistical Methods:	The primary efficacy analyses were to compare Adapalene/Benzoyl Peroxide Gel with Adapalene Monad, Benzoyl Peroxide Monad, and Gel Vehicle on Success Rate and Changes in Inflammatory and Noninflammatory Lesion Count at Week 12 (LOCF, ITT). No adjustment for multiplicity was required. The tests were conducted as two-sided at the 0.05 level. Success Rates at Week 12 (LOCF, ITT) were analyzed by the Cochran-Mantel-Haenszel test stratified by analysis center, using general association statistic. Change in Inflammatory and Noninflammatory Lesion Counts from Baseline to Week 12 (LOCF, ITT) were analyzed by two-way ANCOVA model including Baseline Lesion Counts as a covariate and treatment, analysis center, and treatment-by-Baseline as factors. Treatment-by-center interaction was examined and included in the model if qualitative interaction was detected. The normality assumption was tested using Shapiro-Wilks tests on the residuals from the ANCOVA model. If the normality assumption was not met, then the ranked change in Lesion Count was analyzed by two-way ANCOVA model using ranked baseline count as a covariate, and treatment and analysis center as factors.

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Principal Statistical Methods (Continued):	The secondary analyses of Percent Change in Lesion Count, the tertiary analyses of Change in Investigator's Global Assessment from Baseline, and Subject's Assessment of Acne were performed with the Cochran-Mantel-Haenszel test row mean difference statistic using RIDIT score, stratified by analysis center. The tests were conducted as two-sided at the 0.05 level. All safety data were summarized using the safety population. Local tolerability signs (Erythema, Scaling, Dryness) and symptom (Stinging/Burning) were summarized by severity score. General adverse events (AEs) were tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on MedDRA dictionary.

SUMMARY - CONCLUSIONS

Summary of Results:

Efficacy:

Subject Population: Overall, 87.4% (1459/1670) of subjects completed the study, 211 subjects discontinued early (predominantly due to "subject request" (92/1670, 5.5%) and "lost to follow-up" (79/1670, 4.7%), and only 1.3% (22/1670) of subjects discontinued due to AE. The mean age of subjects was 19.0 years (ranged 12 to 55 years) and 56.2% were female. The majority of subjects were Caucasian (1323; 79.2%), and the remainder were Black (155; 9.3%), Hispanic (97; 5.8%), Asian (63; 3.8%), or other races (32; 1.9%). At Baseline, all groups were comparable with respect to gender, age, race distribution, and skin phototype.

Primary Endpoints: At Week 12 (LOCF, ITT)

- Success Rate (percentage of subjects rated "Clear" and "Almost Clear"): A significantly greater percentage of subjects in the Adapalene/Benzoyl Peroxide Gel group were rated as "Clear" or "Almost Clear", compared with subjects in the Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle groups : 37.9%, 21.8%, 26.7%, and 17.9%, respectively; $p<0.001$.
- Changes in Inflammatory Lesion Counts: The Adapalene/Benzoyl Peroxide Gel showed a greater median reduction of Inflammatory Lesions compared with the Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle groups, 18, 15, 16, and 12, respectively; ($p<0.001$).
- Changes in Noninflammatory Lesion Counts: The Adapalene/Benzoyl Peroxide Gel group showed a significantly greater median reduction of Noninflammatory Lesions compared with the Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle groups: 28, 24, 23, and 18, respectively; $p<0.001$.

Early Treatment Effect: A significant early treatment effect of Adapalene/Benzoyl Peroxide Gel compared with Gel Vehicle was observed starting at Week 1 ($p<0.001$) for all lesion counts (Inflammatory, Noninflammatory, and Total) and Week 2 ($p=0.042$) for Success Rate, and was sustained until the end of the study.

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SUMMARY – CONCLUSIONS (CONTINUED)

Secondary Endpoints: At Week 12 (LOCF, ITT)	• Percent Change in Inflammatory Lesion Counts: The Adapalene/Benzoyl Peroxide Gel group showed a significantly greater mean percent change in Inflammatory Lesion Counts compared with the Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle groups: -61.7%, -50.1%, -52.2%, and -40.8%, respectively; $p<0.001$. • Percent Change in Noninflammatory Lesion Counts: The Adapalene/Benzoyl Peroxide Gel group showed a significantly greater mean percent change in Noninflammatory compared with the Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle groups: -55.6%, -46.0%, -44.1%, and -32.3%, respectively; $p<0.001$. • Percent Change in Total Lesion Counts: The Adapalene/Benzoyl Peroxide Gel group showed a significantly greater mean percent change in Total Lesion Counts compared with the Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle groups: -57.7%, -47.5%, -47.2%, and -35.2%, respectively; $p<0.001$.
Tertiary Endpoints: At Week 12 (LOCF)	• Investigator's Global Assessments: Adapalene/Benzoyl Peroxide Gel group showed a significantly greater percentage improvement in IGA compared with the Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle groups: 74.9%, 62.4%, 58.8%, and 52.6%, respectively; $p\leq0.001$. • Subjects Assessment of Acne: Adapalene/Benzoyl Peroxide Gel was rated by subjects as significantly superior in complete, at least marked, and at least moderate improvement compared with Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle: 78.5%, 70.7%, 66.8%, and 56.3%, respectively; $p\leq0.006$.
Other Endpoints:	• Dermatology Life Quality Index/Children's Dermatology Life Quality Index (DLQI/CDLQI): Results were similar among all groups. • Appreciation Questionnaire: Adapalene/Benzoyl Peroxide Gel was rated as more effective (Question No. 2) than Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle: 70.8%, 61.7%, 58.2%, and 45.3%, respectively. Subject's overall satisfaction (Question No. 4) also showed Adapalene/Benzoyl Peroxide Gel satisfied or very satisfied a higher number of subjects than Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle: 75.6%, 67.3%, 61.8%, and 55.7%, respectively. Subject's self-perceptions (Question No. 5) improved more with Adapalene/Benzoyl Peroxide Gel than with Adapalene Gel, Benzoyl Peroxide Gel, or Gel Vehicle: 77.7%, 71.5%, 69.6%, and 58.2%, respectively.
Examination of Subgroups:	Subgroup analyses of Success Rate and Change in Inflammatory and Noninflammatory Lesion Counts by gender, race, and age group showed Adapalene/Benzoyl Peroxide Gel was consistently more effective than the Monads and Gel Vehicle in all subgroups.
Subjects Taking Hormonal Contraceptives:	For the subgroup of subjects using hormonal contraceptives (i.e., 116 subjects using hormonal contraceptives of which 7 subjects specifically used Ortho-Tricyclen and Estrostep) analyses of Success Rate and Change in Inflammatory and Noninflammatory Lesion Counts were inconclusive due to the small numbers of subjects.

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SUMMARY – CONCLUSIONS (CONTINUED)

SAFETY:

Overall incidence of AEs, Death, SAEs, and AEs Leading to Discontinuation: The numbers of subjects with at least one AE were similar across the study treatments: 199 (47.5%), 162 (38.8%), 137 (33.0%), and 115 (27.5%) for the Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide, and Gel Vehicle groups, respectively. No deaths occurred in this study. Nine (9) SAEs were experienced by seven subjects (all unrelated to study treatment), three subjects in the Adapalene/Benzoyl Peroxide Gel group, one in the Adapalene Gel group, one in the Benzoyl Peroxide Gel group, and two in the Gel Vehicle group. A low incidence (22 of 1670 subjects, 1.3%) of AEs leading to discontinuation, mostly caused by the well-known irritative properties of adapalene and benzoyl peroxide, was observed. The number of subjects with AEs leading to discontinuation was higher with Adapalene/Benzoyl Peroxide Gel compared with Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle: 11 (2.6%), 1 (0.2%), 6 (1.4%), and 4 (1.0%), respectively.

Related AEs: The majority of 'related' AEs were dermatologic, mild to moderate in severity and resolved without residual effects. The incidence of subjects with related AEs across the treatments Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle were: 131 (31.3%), 81 (19.4%), 54 (13.0%), and 34 (8.1%), respectively. Dry skin was the most frequent AE related to treatment which occurred with comparable frequencies in the Adapalene/Benzoyl Peroxide Gel and Adapalene Gel groups, but was slightly lower in the Benzoyl Peroxide Gel and Gel Vehicle groups (21.2%, 14.1%, 8.4%, and 5.3% respectively). Application site burning occurred as the second most frequent event in Adapalene/Benzoyl Peroxide Gel the Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle groups at 15 (3.6%), 3 (0.7%), 1 (0.2%), and 1 (0.2%), respectively.

Severe AEs: Most of the AEs observed in this study were mild or moderate in severity and very few were severe. A total of 17 subjects reported 20 severe AEs. The incidence of severe AEs is comparable between the four groups: 5 (1.2%), 2 (0.5%), 4 (1.0%) and 6 (1.4%) for the Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle treated groups, respectively. Most of the severe AEs were most likely caused by the well-known irritative properties of both Adapalene and Benzoyl Peroxide.

Local Tolerability: Local Tolerability was assessed by scoring of: Erythema, Scaling, Dryness, and Stinging/Burning. Overall, more subjects in the Adapalene/Benzoyl Peroxide Gel group experienced those signs and symptoms compared with the other groups. However, signs and symptoms of local tolerability were transient (i.e., most pronounced during the first two weeks of treatment) and mostly mild to moderate severity with few being recorded as severe.

Sunburn: Nine subjects (0.5%) reported sunburn as an AE: Adapalene/Benzoyl Peroxide Gel (5 subjects); Adapalene Gel (2 subjects); Benzoyl Peroxide Gel (no subjects); and Gel Vehicle (2 subjects). Most of the cases of sunburn occurred during the first three weeks of the study in subjects in the Southwest United States between 2 June 2007 and 16 August 2007. All were mild to moderate in severity. None of

	the reported cases of sunburn were serious or led to permanent discontinuation. All cases of sunburn were reported as resolved while still on treatment.

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	SUMMARY – CONCLUSIONS (CONTINUED)
Adverse Events of Special Interest:	Three (3) suspected sensitization events occurred: Two in the Adapalene/Benzoyl Peroxide Gel group and one in the Benzoyl Peroxide Gel group. One subject was confirmed to have been sensitized to Adapalene/Benzoyl Peroxide Gel but the causal ingredient(s) were not determined by further rechallenge. Another subject was shown not to have been sensitized to Adapalene/Benzoyl Peroxide Gel. The sensitization of a third subject to Benzoyl Peroxide Gel could not be determined by rechallenge.
Pregnancy:	A total of seven (7) pregnancies were reported during this study; of those, two (2), three (3), and two (2) pregnancies occurred in Adapalene-, Benzoyl Peroxide-, and Gel Vehicle-treated subjects, respectively. No safety signals emerged from the pregnancy reports collected in this study.
Conclusions:	Adapalene/Benzoyl Peroxide Gel is a safe and effective, once-daily, nonantibiotic treatment for patients with acne vulgaris. Adapalene/Benzoyl Peroxide Gel provided a clinically meaningful and statistically significant benefit with each component of the fixed combination contributing to the claimed effect. Adapalene/Benzoyl Peroxide Gel has a favorable benefit/risk ratio comparable to Adapalene Gel and Benzoyl Peroxide Gel.
Date of this Report:	**11 August 2008**