CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-769

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA #:	50,769/3S
Applicant:	Dermik Laboratories, Inc.
Name of Drug:	Benzamycin [redacted] erythromycin 3% and benzoyl peroxide 5% gel)
Indication:	Treatment of moderate to moderately-severe acne vulgaris
Route of Administration:	Topical twice daily
Documents Reviewed:	Volumes 1, 11-21 submitted on 01/26/00
Related IND/NDA:	IND 12,193
Medical Officer:	Brenda Vaughan, M.D. (HFD-540)
Statistical Reviewer:	Shiowjen Lee, Ph.D. (HFD-725)

I. Introduction:

Benzamycin Topical Gel (a 3% erythromycin / 5% benzoyl peroxide combination product) was approved and has been marketed as a treatment of acne vulgaris in the US since 1985. The sponsor's current submitted drug application, benzamycin dual pouch, is a modification of the original formulation and claimed to be non-inferior to benzamycin topical gel currently marketed. According to the Sponsor, the dual pouch product does not require refrigeration or compounding as benzamycin topical gel. The product is designed for topically twice-daily use for eight-week treatment of moderate to moderately severe acne vulgaris.

Two pivotal studies (protocols #9709 and 9723) were included in the submission. The objectives of the pivotal studies were to demonstrate that

- benzamycin dual pouch is superior to placebo dual pouch;
- benzamycin dual pouch treatment is non-inferior to the currently marketed topical gel.

At the end-of-phase 2 meeting with the Sponsor on October 23, 1997, the Division recommended that two well-controlled clinical studies which demonstrate that the active dual pouch formulation is significantly more effective than the dual pouch vehicle are acceptable for NDA submission. This was in the consideration that if the results of Study #9709 demonstrated superiority of the active dual pouch to vehicle but inferiority to the marketed topical gel, then the second study demonstrating superiority of benzamycin [redacted] to vehicle would be required for NDA submission.

II. Study Design:

Both studies were designed as double-blind, randomized, parallel-group, and multicenter (6 and 4 centers in studies #9709 and 9723, respectively) conducted in the US. According to the Sponsor, the studies enrolled subjects who are male or non-pregnant and non-nursing female, 13 years of age or older, and satisfy the study inclusion criteria. Eligible subjects were randomized in a ratio of 3:1:3:1 to four treatments (benzamycin [redacted] placebo dual pouch, benzamycin topical gel and placebo topical gel) in Study #9709 and in a ratio of 1:1 to two groups

[redacted] and placebo dual pouch) in Study #9723. Treatment duration was 8 weeks. Clinical evaluation was assessed at Week 2, 4, 6, and 8, where Week 8 was the primary time point.

Efficacy Variables/Statistical Methods Specified in the Protocols:
The efficacy variables specified in the protocols are:

Primary efficacy variables:
- lesion reduction from baseline (including lesion number and percent reduction) in comedone, inflammatory and total (comedone + inflammatory) lesions
- dichotomized Physician's Global Acne Severity evaluation -- ***treatment success***, which was defined as Physician's global acne severity score of either 0 or 0.5 on a 0 to 4 scale with increments of 0.5.

Secondary efficacy variables:
- physician's global acne severity score
- facial oiliness score
- patient's rating in global improvement
- patient's rating of treatment acceptability

Physician's global acne severity assessment was scored at each visit (baseline and Week 2, 4, 6 and 8) based on a 9-point scale:

0 = clear; no inflammatory lesions
0.5 = sparse comedones, with very few or no inflammatory lesions present
1 = comedones, with some small inflammatory lesions present; minimal erythema
1.5 = comedones with an increasing number of inflammatory lesions compared to grade 1
2 = comedones, a moderate number of small inflammatory lesions extending over a wide area of the face; erythema is increasing
2.5 = comedones, an increasing number of inflammatory lesions vs. grade 2, with some larger inflamed lesions
3 = numerous comedones, papules, and pustules with larger inflamed lesions extending over much of the face; erythema may be pronounced
3.5 = comedones, with profuse papulopustular lesions with numerous large inflammatory lesions; some deep, pustular lesions may be present
4 = patient had severe or cystic (nodular) acne and was excluded from this study

The degree of facial oiliness was assessed at each visit based on a 4-point scale below:

0 = none
1 = mild; slight shine on a limited area of the face
2 = moderate; shine clearly evident over entire face
3 = severe; facial oiliness is excessive requiring removal more than once per day

The patient's global improvement score was obtained on the final visit based on a 4-point scale:
0 = no change or worse; 1 = somewhat better; 2 = better; and 3 = much better

Patient's rating of treatment acceptability was also evaluated on the final visit.

Statistical methods specified in the protocols:

- analysis of covariance (ANCOVA) for lesion reduction, general model (GENMOD) for binary outcomes, logistic and Cochran-Mantel-Haenszel (CMH) statistics stratified by study sites for global assessment were planned in the protocols and used in the analyses.
- 90% confidence interval was planned for non-inferiority assessment. The protocols considered that the non-inferiority is established if the lower bound of the confidence interval of mean difference (test drug – active control) is greater than –20% of the active control mean or lower bound of the confidence interval of the ratio of proportions is larger than 80%.

Subjects enrolled and population analyzed in the Sponsor's submission:

- total of 327 and 223 subjects were enrolled in the pivotal studies #9709 and #9723, respectively. Sponsor's intent-to-treat (ITT) analysis included all subjects recruited, while the efficacy-evaluable analysis (which is equivalent to the per-protocol (PP) analysis) consisted of 300 and 193 subjects, respectively.

Reviewer's Comments:

1. According to the study protocols, the enrolled patients at baseline were to:
   (a) have a minimum score of 1.5 on the global acne severity scale;
   (b) have at least 15 and no more than 80 facial inflammatory lesions;
   (c) have at least 20 and no more than 140 facial comedones;
   (d) have no more than 2 facial nodules/cysts;
   (e) ages 13 years and older.

However, total of 20 and 6 subjects did not meet the above inclusion criteria in Study #9709 and, Study #9723, respectively.

The ITT population in this review is defined as all randomized subjects who satisfied the study entry criteria and were dispensed drug medication. Patients who met inclusion criteria and who did not have major protocol deviations constitute the PP population in this review. All subjects recruited are considered in the safety assessment.

2. As suggested by the Agency at the end-of-phase 2 meeting (October 23, 1997), transformation of lesion count data is not recommended for analysis because it is difficult to interpret the results. If the lesion reduction shows a significant deviation from normality, the Agency recommended the use of a non-parametric method rather than carrying transformation on the data.

However, the Sponsor applied the logarithm transformation to the data on lesion proportional reduction prior to the statistical analysis in the submission.

In this review, the analysis of non-normal continuous data is based on analysis of variance (ANOVA) applied to ranks, as well as the Wilcoxon rank sum test. The ANOVA model includes study site, and treatment as factors. The effect of treatment by site interaction is tested at a significance level of 0.10. The analysis of the lesion count reduction also includes the baseline

lesion as a covariate. Similarly, the analysis of the physician's global acne severity score and facial oiliness score also includes baseline score as a covariate.

3. Following the Agency's current policy on the therapeutic non-inferiority assessment, this review uses one-sided 97.5% confidence interval approach. For interval of the mean difference, the non-inferiority limit 20% of the reference mean (i.e. active topical gel) is used. The non-inferiority limit which is usually used for proportion of success is as follows: 20%, 15% and 10% if the success rate for the reference drug is < 80%, 80% – 90%, and >=90%, respectively. The non-inferiority of the test drug is established if the lower bound of the interval is above the negative of the non-inferiority limit.

4. The ITT (defined in comment #1) analysis with the last observation carry forward (LOCF) method is used as the primary analysis for superiority trials in this review, while the PP analysis with LOCF is used to establish the non-inferiority.

III. Results:

Disposition of Subjects

Table 1(a) presents the number and percentage of patients in the ITT and PP populations for each study in this review. The numbers of subjects with violation of protocols or/and excluded from the PP population are also presented. Table 1(b) presents details on the number of patients with violation of the inclusion criteria in each study.

Table 1 (a): Patient Disposition in Study #9709 and #9723

Population	Study #9709					Study #9723		
	AD	PD	AG	PG	Total	AD	PD	Total
All subjects recruited	124	42	121	40	327	112	111	223
Excluded from ITT:								
• inclusion criteria violation	5 (4%)	4 (9.5%)	8 (6.6%)	3 (7.5%)	20	3 (2.7%)	3 (2.7%)	6
ITT population (in this review)	119 (96%)	38 (90.5%)	113 (93.4%)	37 (92.5%)	307	109 (97.3%)	108 (97.3%)	217
Excluded from PP:								
• inclusion criteria violation	5	3	6	1	15	3	3	6
• < 25 days treatment	5	2	3	1	11	11	13	24
• < 25days treatment and inclusion criteria violation	0	1	2	2	5	0	0	0
• violate one or more than one of the following: missed >30% application; <25 days treatment; non-compliant	3	3	3	2	11	3	3	6
PP population (in this review)	111 (90%)	33 (79%)	107 (88%)	34 (85%)	285	95 (85%)	92 (83%)	187

AD = active dual pouch; PD = placebo dual pouch; AG = active gel; PG = placebo gel
Source: summary is based on the Sponsor's NDA submission Volumes 14 and 17.

Table 1 (b): Subjects with Violation of Inclusion Criteria

Violation of Entry criteria	Study 9709				Study 9723	
	AD (n=124)	PD (n=42)	AG (n=121)	PG (n=40)	AD (n=112)	PD (n=111)
Age < 13	1	0	1	0	0	0
Comedones <20 or > 140	2	2	3	2	1	2
Inflammatory <15 or > 80	1	0	2	1	2	0
Physician global <1.5	1	2	2	0	0	1
Subtotal	5 (4%)	4 (9.5%)	8 (6.6%)	3 (7.5%)	3 (2.7%)	3 (2.7%)
Study Total	20				6	

AD = active dual pouch; PD = placebo dual pouch; AG = active gel; PG = placebo gel
Source: summary is based on the Sponsor's NDA submission Volumes 14 and 17.

The results of Table 1(a)-1(b) suggest that,

- no significant difference between treatment groups is indicated in each study with respect to the subject inclusion in the ITT and PP populations, and the percentage of subjects with violation of study entry criteria.

Demographics and Baseline Characteristics

The demographics and baseline characteristics of the ITT population are presented in Table A1.1 of the Appendix. No significant difference between treatments is suggested (p-value $\geq$ 0.099 and p-value $\geq$ 0.126 for Study #9709 and #9723, respectively).

III.1. Efficacy Results in Study #9709

Treatment Arms:
- active dual pouch (AD)
- active topical gel (AG)
- placebo dual pouch (PD)
- placebo topical gel (PG)

Study Objectives:
i. active dual pouch is superior to placebo dual pouch
ii. active dual pouch is non-inferior to active topical gel

Lesion Reduction

The normality assumption of lesion reduction from baseline to Week 8 has been examined using Shapiro-Wilks test. The resulting p-value indicates non-normality of lesion reduction. Consequently, this review carried out efficacy analyses based on (a) ANOVA, (b) ANOVA applied to ranks, and (c) Wilcoxon rank sum test. The results of these analyses were consistent. This review reports the results based on ANOVA applied to ranks of lesion reduction for superiority comparison.

Table 2 presents the lesion reduction (including absolute number and percent reduction) from baseline to Week 8 between treatments. The supporting analysis of lesion reduction at Week 2, 4 and 6 is summarized in Table A2.1 of the Appendix.

Table 2: Comparison of Lesion Reduction from Baseline to Week 8: Study #9709

	Comedone Lesions					
	AD	**AG**	**PD**	**PG**	**comparison**	**p-value**
Mean # lesion reduction	24.0	23.3	14.6	13.9	**AD vs. PD**	0.003
Mean lesion % reduction	45.9%	42.8%	24.4%	20.2%	**AD vs. PD**	< 0.001
	Inflammatory Lesions					
Mean # lesion reduction	13.5	11.9	4.3	6.5	**AD vs. PD**	< 0.001
Mean lesion % reduction	49.1%	45.4%	16.8%	27.6%	**AD vs. PD**	< 0.001
	Total Lesions (Comedone + Inflammatory)					
Mean # lesion reduction	37.4	35.2	18.9	20.4	**AD vs. PD**	< 0.001
Mean lesion % reduction	48.1%	43.8%	22.2%	25.8%	**AD vs. PD**	< 0.001

AD = active dual pouch; PD = placebo dual pouch; AG = active topical gel; PG = placebo topical gel

The results of Table 2 can be summarized by

- Active dual pouch (AD) is significantly more effective than placebo dual pouch (PD) in comedone, inflammatory and total lesion reduction at Week 8 (p-value$\leq$ 0.003).

To discuss the non-inferiority of active dual pouch (AD) with respect to active topical gel (AG) in lesion reduction at Week 8, we need to calculate the lower bounds of 97.5% confidence intervals of mean difference (AD mean – AG mean). This is given below.

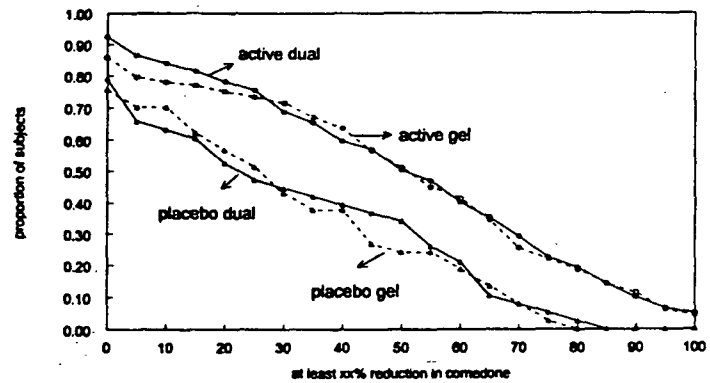
Lesion type	Lower bound of 97.5% CI	–20% of Active topical gel mean
Comedone		
Lesion # reduction	–4.9	–4.9
Lesion % reduction	–6.3%	–8.8%
Inflammatory		
Lesion # reduction	–1.2	–2.5
Lesion % reduction	–5.3%	–9.3%
Total (comedone + inflammatory)		
Lesion # reduction	–4.7	–7.3
Lesion % reduction	–3.0%	–9.0%

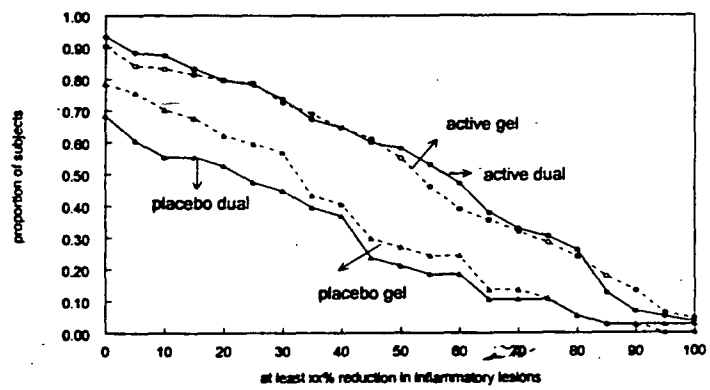
The findings of the table are:

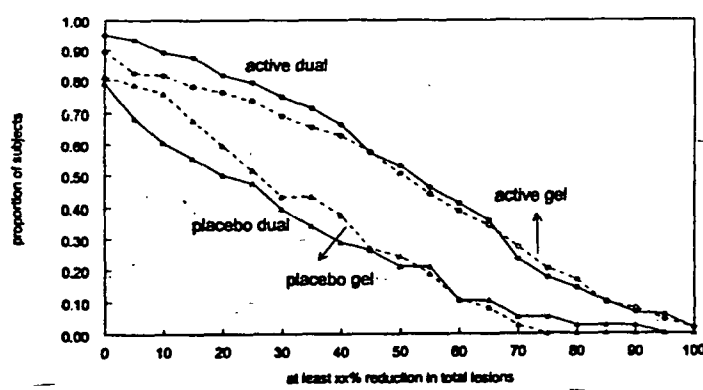
- Active dual pouch is non-inferior to active topical gel in the lesion reduction at Week 8 since the lower bounds of the 97.5% confidence interval for mean difference are all on and above –20% of active topical gel mean.

Supporting analysis is performed in terms of the proportion of subjects with at least xx% lesion reduction from baseline to Week 8, where xx = 0 – 100. Figure 1 below shows the plot and numerical comparison is summarized in Table A2.2 of the Appendix.

Figure 1: Comparison of the Proportion of Subjects with at Least xx% Reduction in Comedone, Inflammatory and Total Lesions at Week 8, where xx=0-100: Study #9709







The results of the proportion of subjects with at least xx% lesion reduction can be summarized by the following:

- Active dual pouch has relatively higher proportion of subjects with at least xx% lesion reduction than placebo dual pouch (Figure 1) and statistically significant results in most comparisons (Table A2.2).
- Active dual pouch and active topical gel arms are comparable (i.e. bands are overlapping in Figure 1) and statistically non-inferior with respect to active topical gel (Table A2.2).

Treatment Success

Both CMH test and GENMOD model were used to analyze the treatment success in physician's global acne severity assessment. Since the analysis results based on the various methods are consistent, this review reports the results of the CMH test. Table 3 summarizes the number (and percentage) of subjects with treatment success at Week 8 and comparison. The supporting analysis at Week 2, 4 and 6 is presented in Table A2.3 of the Appendix.

Table 3: Treatment Success at Week 8: Study #9709

Treatment				Comparison	
AD (n=119)	AG (n=113)	PD (n=38)	PG (n=37)	AD vs. PD (p-value)	Lower bound of 97.5% CI
33 (27.7%)	30 (26.5%)	1 (2.6%)	4 (10.8%)	< 0.001	−11.2%

AD = Active dual pouch; AG = active topical gel; PD = Placebo dual pouch; PG = placebo topical gel.

The results of Table 3 can be summarized by:

- Active dual pouch is significantly more effective than placebo dual pouch in achieving treatment success at Week 8 (p-value < 0.001). It is non-inferior with respect to active topical gel since the lower bound of the 97.5% confidence interval for percent difference (i.e. −11.2%) is above −20%.

Note that the non-inferiority of active dual pouch with respect to active topical gel in Sponsor's submission is not concluded. It should be noted that the Sponsor used the interval on the difference of the logarithm proportion to assess non-inferiority. However, transformation on the data for efficacy evaluation is not suggested.

Secondary Efficacy Variables:

The analyses in the physician's global acne severity score, facial oiliness score, and patient's global assessment of improvement as well as treatment acceptability are summarized in Table A2.4-A2.6 of the Appendix, respectively. The findings are:

- Active dual pouch group has significantly lesser mean severity acne score (p-value < 0.001, Table A2.4) and smaller mean facial oiliness score (p-value < 0.001, Table A2.5) than placebo at Week 8. The non-inferiority with respect to active topical gel is concluded since the 97.5% confidence bounds are within 20% of the active topical gel mean limit.

- Active dual pouch is superior to placebo in patient's rating of improvement and treatment acceptability (p-value $\leq$ 0.005, Table A2.6). It is not inferior to active gel in the global evaluation score since the lower bound of confidence interval is above –20% of active topical gel mean. The non-inferiority is also concluded for the proportions of subjects rating improvement of '*somewhat better and above*' and treatment acceptability since the lower limits of 97.5% confidence intervals of percent difference are above –10%.

It should be noted that the non-inferiority of active dual pouch to active topical gel relative to the treatment acceptability is not concluded in Sponsor's submission. This is because that the Sponsor's result was based on the interval of the difference of logarithm proportion (i.e. logarithm of proportion ratio) which is not appropriate in therapeutic efficacy evaluation.

Subgroup Efficacy Analyses

Subgroup efficacy analyses by age (pediatrics vs. adults), gender, and race (Caucasian, Black and others) are presented in Table A2.7-A2.9 of the Appendix. The efficacy results are generally consistent. Placebo dual pouch may show numerical effectiveness in lesion reduction for some subgroups (e.g. Black and Others races). However, the sample sizes in these subgroups are relatively small. Thus, it can be concluded no significant effect in the subgroup.

Reviewer's Conclusion on Study #9709:

- active dual pouch (AD) is superior to placebo dual (PD), and non-inferior to active topical gel (AG) for 8-week treatment of moderate to moderately severe acne vulgaris in:
  - reduction of comedone, inflammatory and total lesions;
  - achieving treatment success which is defined as physician's global acne severity score of 0 or 0.5.
  - reducing physician's acne severity score and facial oiliness score; better patient's rating of improvement; and treatment acceptability.

III.2. Efficacy Results in Study #9723

Treatment Arms:
- active dual pouch (AD)
- placebo dual pouch (PD)

Study Objective: active dual pouch is superior to placebo dual pouch

Lesion Reduction

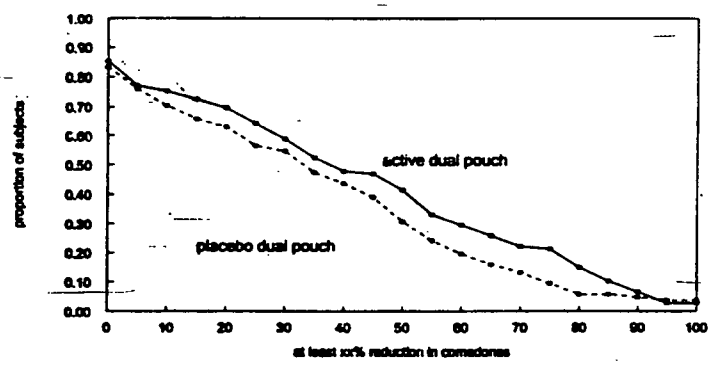
The lesion reduction in AD and PD arms at Week 8 and comparison is summarized in Table 4 below. The supporting analysis of lesion reduction at Week 2, 4, and 6 is presented in Table A3.1 of the Appendix. The results in Table 4 suggest that active dual pouch (AD) is significantly superior to placebo (PD) in the reduction of inflammatory and total lesions at Week 8 (p-value $\leq$ 0.002). However, it is ***not*** significantly better than placebo in comedone lesion reduction since p-value $\geq$ 0.175.

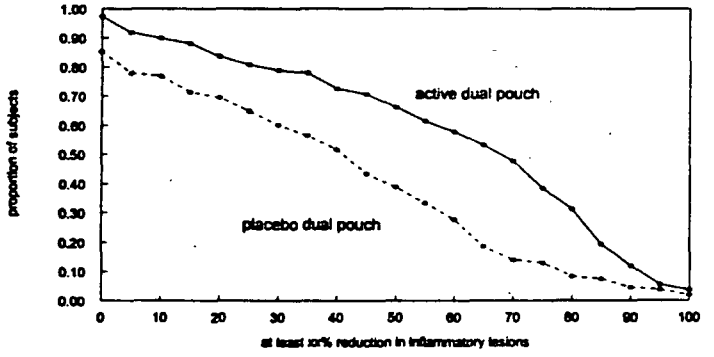
Table 4: Comparison of Lesion Reduction at Week 8: Study #9723

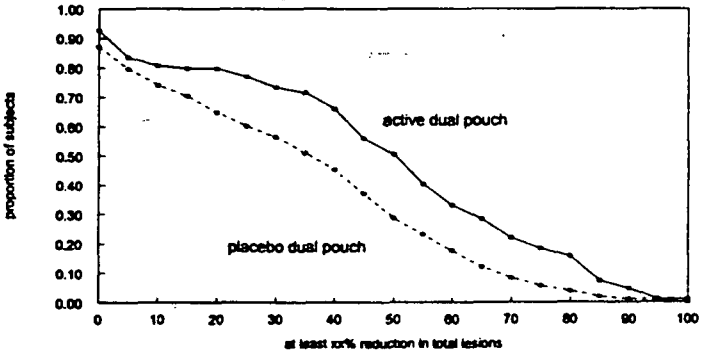
	Treatment		
Lesion Reduction	**Active Dual (n=109)**	**Placebo Dual (n=108)**	**p-value**
	Comedone lesion		
number reduction	15.07	12.82	0.262
% reduction	36.2%	29.6%	0.175
	Inflammatory lesion		
number reduction	16.63	9.44	< 0.001
% reduction	57.2%	34.1%	< 0.001
	Total lesion (comedone + inflammatory)		
number reduction	31.71	22.27	0.002
% reduction	45.3%	31.4%	< 0.001

As a supporting analysis, Figure 2 plots the proportion of subjects with at least xx% lesion reduction, where xx ranges from 0 to 100. The numerical comparison is summarized in Table A3.2 of the Appendix.

Figure 2: Comparison of the Proportion of Subjects with at Least xx% Reduction in Comedone, Inflammatory and Total Lesions at Week 8, where xx=0-100: Study #9723







The findings in terms of the proportion of subjects with at least xx% lesion reduction are:

- relatively higher proportion of subjects with at least xx% lesion reduction under active dual pouch treatment is observed (Figure 2).
- Active dual pouch is significantly superior to placebo in the reduction of inflammatory and total lesions but ***not*** in comedone lesion reduction in most comparisons (Table A3.2).

Treatment Success

Table 5 below presents the comparison of the number (percentage) of subjects with treatment success at Week 8. The supporting analysis at Week 2, 4, and 6 is summarized in Table A3.3 of the Appendix.

Table 5: Treatment Success at Week 8: Study #9723

Treatment		
Active Dual (n=109)	**Placebo Dual (n=108)**	**p-value**
39 (35.8%)	13 (12.0%)	< 0.001

The results of Table 5 suggest that active dual pouch is significantly more effective than placebo in achieving treatment success at Week 8 (p-value < 0.001).

Secondary Efficacy Variables:
The analyses of physician's global acne severity score, facial oiliness score, patient evaluation of improvement, and treatment acceptability are presented in Table A3.4-A3.6 of the Appendix.

- active dual pouch is significantly more effective than placebo in reducing the physician's global acne severity score at Week 8 (p-value <0.001, Table A3.4).
- the two treatments are ***marginally not*** significantly different in the mean facial oiliness score at Week 8 (p-value = 0.062, Table A3.5).
- Active dual pouch is superior to placebo in the mean patient global evaluation score (p-value = 0.002, Table A3.6); proportions of subjects who rated global improvement as '*somewhat better and above*' and treatment acceptability (p-value ≤ 0.010, Table A3.6).

Note that Sponsor concluded a significant difference between treatments in the facial oiliness score at Week 8 (p-value = 0.026). Their analysis was based on CMH test stratified by study sites without the consideration of baseline oiliness score. This review uses ANOVA on the ranked data with the inclusion of baseline score, where the effect of baseline score on the oiliness score at Week 8 is shown to be significant (p-value < 0.001).

Subgroup Efficacy Analyses
For subgroup efficacy analysis by age (pediatrics and adults), gender, and race (Caucasian, Black and Others), the summary in Table A3.7-A3.9 of the Appendix generally suggests the consistency of the results. No significant subgroup effect is indicated.

Reviewer's Conclusion on Study #9723:

- active dual pouch (AD) is superior to placebo dual (PD) for 8-week treatment of moderate to moderately severe acne vulgaris in
  - reduction of inflammatory and total lesions;
  - treatment success which is defined as physician's global acne score of 0 or 0.5;
  - reduction of physician's acne severity score; patient's rating of improvement and treatment acceptability

  However, active dual pouch is ***not*** significantly better than placebo in
  - comedone lesion reduction;
  - facial oiliness score reduction.

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IV. Safety Assessment:

Safety assessment of active and placebo treatments based on

(a) extent of exposure to the test medication; and

(b) adverse events, serious adverse events and withdrawals due to adverse events

is summarized in Table 6 and 7 below, respectively. Data presented are based on two pivotal studies combined (Study #9709 and #9723), a total of 550 subjects.

(a). Extent of Exposure

Table 6 presents the extent of exposure to study medication in regards to the duration of treatments.

Table 6: Extent of Exposure to Study Medication

	Treatment Group			
Duration of Treatment (in days)	**AD (n=236)**	**PD (n=153)**	**AG (n=121)**	**PG (n=40)**
Mean	53.2	51.2	54.1	52.7
# of subjects (%) exposed to study drug within:				
1-15 days	230 (97.5%)	146 (95.4%)	118 (97.5%)	39 (97.5%)
16-29 days	222 (94.1%)	142 (92.8%)	115 (95%)	37 (92.5%)
30-36 days	217 (92%)	132 (86.3%)	113 (93.4%)	36 (90%)
37-43 days	216 (91.5%)	129 (84.3%)	113 (93.4%)	36 (90%)
44-53 days	215 (91%)	128 (83.7%)	112 (92.6%)	35 (87.5%)
54-60 days	205 (86.9%)	123 (80.4%)	107 (88.4%)	34 (85%)
beyond 60 days	19 (8%)	15 (10%)	12 (10%)	4 (10%)

AD = active dual pouch; PD = placebo dual pouch; AG = active topical gel; PG = placebo topical gel
Source: summary is based on Sponsor's NDA submission (Volume 21, pages 8-11-58 and 8-11-59)

- no significant difference is indicated between active dual pouch and active gel arms in the mean number of exposure days, and percentage of subjects exposed to study medication within the study time window.

(b). Adverse Events, Deaths, Serious AEs, and Withdrawals due to AEs

Table 7 below presents the incidence, intensity and relationship of adverse events to study drug. The results can be summarized by:

- no significant difference in regards to the incidence of adverse events between active dual pouch (AD) and active topical gel (AG) is indicated
- approximately 1.3% of subjects in active dual pouch (AD) arm experienced serious adverse events comparing to other treatments with none occurrence. However, the result is not significant (p-value = 0.162 and 0.214 comparing to placebo dual and active topical gel groups, respectively, based on CMH test).

Table 7: Adverse Events: Number of subjects (%)

	Treatment			
Event	**AD (n=236)**	**PD (n=153)**	**AG (n=121)**	**PG (n=40)**
Adverse events incidence	81 (34%)	42 (27%)	43 (36%)	13 (33%)
Total adverse event occurrence	132	72	56	13
Adverse event related to study drug by relationship:				
Possible: total events	7	7	6	0
# of subjects (%)	5 (2%)	3 (2%)	5 (4%)	0
Probable: total events	23	9	2	0
# of subjects (%)	17 (7%)	6 (4%)	2 (2%)	0
Definite: total events	9	1	3	0
# of subjects (%)	7 (3%)	1 (< 1%)	3 (2%)	0
Adverse event by intensity:				
UNK/NA: total events	1	0	2	0
# of subjects (%)	1 (< 1%)	0	2 (2%)	0
Mild: total events	64	40	25	6
# of subjects (%)	34 (14%)	19 (12%)	17 (14%)	6 (15%)
Moderate: total events	62	29	27	7
# of subjects (%)	41 (17%)	20 (13%)	22 (18%)	7 (18%)
Severe: total events	5	3	2	0
# of subjects (%)	5 (2%)	3 (2%)	2 (2%)	0
Serious adverse event	3 (1.3%)	0	0	0
Deaths	0	0	0	0
Adverse event resulting in study discontinuation	1 (< 1%)	1 (< 1%)	0	0

AD = active dual pouch; PD = placebo dual pouch; AG = active topical gel; PG = placebo topical gel
Source: summary is based on Sponsor's NDA submission (Volume 21, pages 8-11-63 to 8-11-72)

V. Summary and Conclusion:

Efficacy:

The Sponsor in this submission presented results for two pivotal studies (Study #9709 and #9723) in supporting the efficacy and safety claim for benzamycin ——— to be administered twice daily for 8-week treatment of moderate to moderately-severe acne vulgaris. Efficacy results from these studies based on LOCF for missing data can be summarized as follows.

Benzamycin ——— is significantly more effective than placebo dual pouch in:

- reduction of inflammatory and total lesions
- achieving treatment success
- reducing physician's global acne severity score
- patients rating of improvement, and treatment acceptability

However, benzamycin ——— is NOT significantly better than placebo in:

- reduction of comedone lesion (Study #9723 failed)
- facial oiliness score reduction (Study #9723 failed)

For non-inferiority assessment in Study #9709, the analyses suggest that benzamycin ——— is non-inferior to benzamycin topical gel currently marketed.

A summary of the efficacy results with respect to the primary and secondary efficacy variables, respectively, is given below:

Primary efficacy variables:

		Lesion Reduction			
Pivotal Study	Comparison	comedone	inflammatory	Total lesions	Treatment success
Study #9709	AD vs. PD AD vs. AG	superior * non-inferior *	superior * non-inferior *	superior * non-inferior *	superior * non-inferior @
Study #9723	AD vs. PD	NOT significant *	superior *	superior *	superior *

Secondary efficacy variables:

		Secondary Efficacy Parameter			
Pivotal Study	Comparison	global acne severity score	facial oiliness score	patient's rating of improvement	treatment acceptability
Study #9709	AD vs. PD AD vs. AG	superior * non-inferior *	superior * non-inferior +	superior * non-inferior *	superior * non-inferior @
Study #9723	AD vs. PD	superior *	NOT significant @	superior *	superior *

AD = active dual pouch; PD = placebo dual pouch; AG = active topical gel
* conclusion in this review is consistent to Sponsor's submission
@ conclusion in this review differs from Sponsor's submission
+ only p-value but not interval assessment provided in Sponsor's submission since not set a priori in study protocol

Safety:
The two pivotal studies suggest that active dual pouch has similar safety profile to active topical gel currently marketed in regards to the extent of drug exposure and incidence of adverse events.

/S/

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APPENDIX

Table A1.1: Comparison of Subjects Demographics and Baseline Characteristics

	Study #9709					
Variable	Total Population n=307	Active Dual n=119	Placebo Dual n=38	Active Gel n=113	Placebo Gel n=37	p-value[1,2]
Age (All)	19.9±6.5	19.4±6.2	19.6±5.5	20.4±7.5	20.1±5.2	0.515
Pediatric	157 15.1±1.3	64 14.8±1.3	19 14.8±1.3	57 15.3±1.3	17 15.5±1.2	0.099
Adult	150 24.8±6.1	55 24.6±5.5	19 24.3±3.7	56 25.5±7.7	20 24.0±3.9	0.973
Gender						
Female	157 (51.1%)	62 (52.1%)	21 (55.3%)	53 (46.9%)	21 (56.8%)	0.643
Male	150 (48.9%)	57 (47.9%)	17 (44.7%)	60 (53.1%)	16 (43.2%)	
Race						
Caucasian	212 (69%)	82 (69%)	28 (73.7%)	76 (67.3%)	26 (70.3%)	0.943
Black	23 (7.5%)	10 (8.4%)	2 (5.3%)	9 (8%)	2 (5.4%)	
Others	72 (23.5%)	27 (22.7%)	8 (21%)	28 (24.8%)	9 (24.3%)	
Comedone	54.6±27.2	55.1±28.4	55.9±27.9	54.7±27.2	51.1±22.8	0.950
Inflammatory	27.1±12.5	27.6±13.9	26.4±10.3	26.6±11.6	27.3±12.8	0.998
Total lesions	81.6±32.7	82.7±33.4	82.4±34.1	81.3±32.9	78.4±28.7	0.966
Global severity score	2.0±0.5	2.0±0.5	2.0±0.5	2.0±0.5	2.0±0.5	0.979
Facial oiliness	1.7±0.6	1.7±0.6	1.5±0.7	1.7±0.6	1.7±0.6	0.558

	Study #9723			
Variable	Total Population n=217	Active Dual n=109	Placebo Dual n=108	p-value
Age (All)	18.5±5.8	18.7±6.2	18.3±5.5	0.964
Pediatric	133 14.9±1.4	65 14.8±1.3	68 15.1±1.3	0.228
Adult	84 24.2±5.7	44 24.5±6.0	40 23.9±5.4	0.692
Gender				
Female	109 (50.2%)	56 (51.4%)	53 (49.1%)	0.736
Male	108 (49.8%)	53 (48.6%)	55 (50.9%)	
Race				
Caucasian	170 (78.3%)	91 (83.5%)	79 (73.1%)	0.165
Black	30 (13.8%)	12 (11%)	18 (16.7%)	
Others	17 (7.8%)	6 (5.5%)	11 (10.2%)	
Comedone	42.0±23.4	41.8±26.1	42.3±20.4	0.161
Inflammatory	29.8±13.1	30.1±14.3	29.5±11.8	0.892
Total lesions	71.8±27.9	71.9±30.8	71.8±24.8	0.354
Global severity score	2.1±0.5	2.0±0.5	2.1±0.5	0.357
Facial oiliness	1.6±0.7	1.6±0.6	1.7±0.7	0.126

[1]p-value is based on Wilcoxon rank sum test (or Kruskal-Wallis test) in the analysis of continuous data
[2]p-value is based on Cochran-Mantel-Haenszel test stratified by study sites in the analysis of categorical data

Table A2.1: Comparison of Lesion Reduction at Week 2, 4 and 6: Study #9709

Week 2	Comedone Lesions					
	AD	AG	PD	PG	comparison	p-value
Mean # lesion reduction	12.3	9.8	9.4	5.1	AD vs. PD	0.092
Mean lesion % reduction	24.6%	20.6%	13.9%	3.9%	AD vs. PD	0.028
	Inflammatory Lesions					
Mean # lesion reduction	9.6	8.3	3.9	4.4	AD vs. PD	< 0.001
Mean lesion % reduction	34.3%	32.7%	12.5%	18.6%	AD vs. PD	< 0.001
	Total Lesions (Comedone + Inflammatory)					
Mean # lesion reduction	21.9	18.1	13.2	9.5	AD vs. PD	0.007
Mean lesion % reduction	28.8%	25.6%	14.8%	11.3%	AD vs. PD	0.002
Week 4	Comedone Lesions					
	AD	AG	PD	PG	comparison	p-value
Mean # lesion reduction	16.7	15.8	9.2	10.2	AD vs. PD	0.108
Mean lesion % reduction	33.3%	31.1%	15.2%	12.0%	AD vs. PD	0.010
	Inflammatory Lesions					
Mean # lesion reduction	12.1	10.8	4.2	5.3	AD vs. PD	< 0.001
Mean lesion % reduction	43.8%	41.7%	18.0%	22.2%	AD vs. PD	< 0.001
	Total Lesions (Comedone + Inflammatory)					
Mean # lesion reduction	28.8	26.5	13.3	15.6	AD vs. PD	0.004
Mean lesion % reduction	37.9%	35.7%	16.3%	17.6%	AD vs. PD	< 0.001
Week 6	Comedone Lesions					
	AD	AG	PD	PG	comparison	p-value
Mean # lesion reduction	22.5	19.6	14.7	13.1	AD vs. PD	0.025
Mean lesion % reduction	43.4%	38.5%	24.5%	19.3%	AD vs. PD	0.003
	Inflammatory Lesions					
Mean # lesion reduction	13.0	11.6	6.7	5.7	AD vs. PD	< 0.001
Mean lesion % reduction	48.0%	44.2%	27.7%	25.2%	AD vs. PD	0.002
	Total Lesions (Comedone + Inflammatory)					
Mean # lesion reduction	35.5	31.2	21.4	18.8	AD vs. PD	0.002
Mean lesion % reduction	45.8%	40.8%	25.6%	24.0%	AD vs. PD	< 0.001

AD = active dual pouch; AG = active topical gel; PD = placebo dual pouch; PG = placebo topical gel.

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Table A2.2: Comparison of the Proportion of Subjects with at Least xx% Lesion Reduction at Week 8, where xx = 50 –100: Study #9709

	Treatment				Comparison [1]	
At least xx% lesion reduction	AD (n=119)	AG (n=113)	PD (n=38)	PG (n=37)	AD vs. PD (p-value)	lower bound of 97.5% CI of (AD%–AG%)
	Comedone Lesion					
100	6 (5%)	5 (4.4%)	0	0	0.142	–5.1%
90	12 (10.1%)	13 (11.5%)	0	0	0.027	–9.8%
80	23 (19.3%)	21 (18.6%)	1 (2.6%)	0	0.009	–9.6%
70	35 (29.4%)	29 (25.7%)	3 (7.9%)	3 (8.1%)	0.004	–7.6%
60	48 (40.3%)	47 (41.6%)	8 (21.1%)	7 (18.9%)	0.021	–12.9%
50	60 (50.4%)	58 (51.3%)	13 (34.2%)	9 (24.3%)	0.062	–12.5%
	Inflammatory Lesion					
100	4 (3.4%)	5 (4.4%)	1 (2.6%)	0	0.753	–6.4%
90	8 (6.7%)	15 (13.3%)	1 (2.6%)	1 (2.7%)	0.294	–15%
80	31 (26.1%)	27 (23.9%)	2 (5.3%)	2 (5.4%)	0.004	–9.9%
70	39 (32.8%)	36 (31.9%)	4 (10.5%)	5 (13.5%)	0.004	–.1%
60	56 (47.1%)	44 (38.9%)	7 (18.4%)	9 (24.3%)	< 0.001	–3.8%
50	69 (58%)	62 (55%)	8 (21.1%)	10 (27%)	< 0.001	–8.8%
	Total Lesion					
100	2 (1.7%)	2 (1.8%)	0	0	0.405	–3.6%
90	8 (6.7%)	9 (8%)	1 (2.6%)	0	0.279	–8.3%
80	17 (14.3%)	19 (16.8%)	1 (2.6%)	0	0.040	–12.3%
70	28 (23.5%)	31 (27.4%)	2 (5.3%)	1 (2.7%)	0.009	–14.5%
60	49 (41.2%)	44 (38.9%)	4 (10.5%)	4 (10.8%)	< 0.001	–9.1%
50	63 (53%)	57 (50.4%)	8 (21%)	9 (24.3%)	< 0.001	–9.7%

AD = Active dual pouch; AG = active topical gel; PD = Placebo dual pouch; and PG = placebo topical gel.
[1]As a supporting analysis, comparison is intended to be informal as otherwise, one should address the multiplicity issue.

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Table A2.3: Treatment Success at Week 2, 4, and 6: Study #9709

	Treatment				Comparison	
Assessment Week	AD (n=119)	AG (n=113)	PD (n=38)	PG (n=37)	AD vs. PD (p-value)	Lower bound of 97.5% CI
Week 2	4 (3.4%)	2 (1.8%)	0	0	0.192	–3.1%
Week 4	12 (10.1%)	5 (4.4%)	0	0	0.037	–1.6%
Week 6	23 (19.3%)	16 (14.2%)	0	3 (8.1%)	0.002	–5.2%

AD = Active dual pouch; AG = active topical gel; PD = Placebo dual pouch; PG = placebo topical gel.

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Table A2.4: Comparison of Physician's Global Acne Severity Scores: Study #9709

	Treatment				Comparison	
global score	AD(n=119)	AG (n=113)	PD (n=38)	PG (n=37)	AD vs. PD (p-value)	One-Sided 97.5% CI of (AD-AG) and 20% of active control mean
	Week 2					
0	0	0	0	0	0.018	0.09 (0.3)
0.5	4 (3.4%)	2 (1.8%)	0	0		
1.0	22 (18.5%)	17 (15.0%)	4 (10.5%)	8 (21.6%)		
1.5	46 (38.7%)	46 (40.7%)	15 (39.5%)	10 (27.0%)		
2.0	24 (20.2%)	33 (29.2%)	10 (26.3%)	9 (24.3%)		
2.5	14 (11.8%)	12 (10.6%)	7 (18.4%)	6 (16.2%)		
3.0	8 (6.7%)	3 (2.7%)	2 (5.3%)	4 (10.8%)		
3.5	1 (0.8%)	0	0	0		
mean score	**1.71**	**1.70**	**1.84**	**1.84**		
	Week 4					
0	0	0	0	0	< 0.001	0.02 (0.3)
0.5	12 (10.1%)	5 (4.4%)	0	0		
1.0	36 (30.3%)	34 (30.1%)	8 (21.1%)	11 (29.7%)		
1.5	41 (34.5%)	33 (29.2%)	12 (31.6%)	7 (18.9%)		
2.0	16 (13.5%)	34 (30.1%)	7 (18.4%)	10 (27.0%)		
2.5	11 (9.2%)	7 (6.2%)	8 (21.1%)	6 (16.2%)		
3.0	2 (1.7%)	0	3 (7.9%)	3 (8.1%)		
3.5	1 (0.8%)	0	0	0		
mean score	**1.45**	**1.52**	**1.82**	**1.77**		
	Week 6					
0	2 (1.7%)	1 (0.9%)	0	0	0.014	0.09 (0.3)
0.5	21 (17.7%)	15 (13.3%)	0	3 (8.1%)		
1.0	31 (26.1%)	31 (27.4%)	14 (36.8%)	10 (27.0%)		
1.5	33 (27.7%)	40 (35.4%)	11 (29.0%)	7 (18.9%)		
2.0	23 (19.3 %)	17 (15.0%)	4 (10.5%)	8 (21.6%)		
2.5	6 (5.0%)	8 (7.1%)	7 (18.4%)	5 (13.5%)		
3.0	3 (2.5%)	1 (0.9%)	2 (5.3%)	4 (10.8%)		
3.5	0	0	0	0		
mean score	**1.35**	**1.38**	**1.63**	**1.69**		
	Week 8					
0	4 (3.4%)	3 (2.6%)	0	0	**< 0.001**	**0.14 (0.2)**
0.5	29 (24.4%)	27 (23.9%)	1 (2.6%)	4 (10.8%)		
1.0	38 (31.9%)	40 (35.4%)	13 (34.2%)	9 (24.3%)		
1.5	27 (22.7%)	25 (22.1%)	10 (26.3%)	7 (18.9%)		
2.0	15 (12.6%)	13 (11.5 %)	7 (18.4%)	7 (18.9%)		
2.5	3 (2.5%)	4 (3.5%)	5 (13.2%)	9 (24.3%)		
3.0	3 (2.5%)	0	2 (5.3%)	0		
3.5	0	1 (0.9%)	0	1 (2.7%)		
mean score	**1.17**	**1.15**	**1.61**	**1.66**		

AD = Active dual pouch; AG = active topical gel; PD = Placebo dual pouch; and PG = placebo topical gel.

Table A2.5: Comparison of Facial Oiliness Scores: Study #9709

	Treatment				Comparison	
oiliness score	AD(n=119)	AG (n=113)	PD (n=38)	PG (n=37)	AD vs. PD (p-value)	One-Sided 97.5% CI of (AD-AG) and 20% of active control mean
	Week 2					
0	7 (5.9%)	4 (3.5%)	3 (7.9%)	1 (2.7%)	0.002	0.14 (0.26)
0.5	13 (10.9%)	15 (13.3%)	2 (5.3%)	4 (10.8%)		
1.0	39 (32.8%)	39 (34.5%)	12 (31.6%)	13 (35.1%)		
1.5	28 (23.5%)	24 (21.2%)	3 (7.9%)	7 (18.9%)		
2.0	27 (22.7%)	26 (23.0%)	14 (36.8%)	8 (21.6%)		
2.5	3 (2.5%)	5 (4.4%)	2 (5.3%)	4 (10.8%)		
3.0	2 (1.7%)	0	2 (5.3%)	0		
mean score	**1.30**	**1.30**	**1.49**	**1.39**		
	Week 4					
0	14 (11.8%)	10 (8.9%)	3 (7.9%)	1 (2.7%)	0.001	0.15 (0.23)
0.5	15 (12.6%)	17 (15.0%)	2 (5.3%)	7 (18.9%)		
1.0	42 (35.3%)	41 (36.3%)	12 (31.6%)	13 (35.1%)		
1.5	20 (16.8%)	21 (18.6%)	7 (18.4%)	6 (16.2%)		
2.0	24 (20.2%)	22 (19.5%)	10 (26.3%)	8 (21.6%)		
2.5	3 (2.5%)	2 (1.8%)	2 (5.3%)	1 (2.7%)		
3.0	1 (0.8%)	0	2 (5.3%)	1 (2.7%)		
mean score	**1.16**	**1.15**	**1.43**	**1.27**		
	Week 6					
0	8 (6.7%)	8 (7.1%)	4 (10.5%)	1 (2.7%)	0.006	0.17 (0.22)
0.5	22 (18.5%)	27 (23.9%)	3 (7.9%)	5 (13.5%)		
1.0	48 (40.3%)	37 (32.7%)	12 (31.6%)	12 (32.4%)		
1.5	16 (13.5%)	16 (14.2%)	5 (13.2%)	10 (27.0%)		
2.0	21 (17.7%)	22 (19.5%)	11 (28.9%)	5 (13.5%)		
2.5	3 (2.5%)	3 (2.7%)	1 (2.6%)	3 (8.1%)		
3.0	1 (0.8%)	0	2 (5.3%)	1 (2.7)		
mean score	**1.14**	**1.12**	**1.36**	**1.35**		
	Week 8					
0	11 (9.2%)	9 (8%)	4 (10.5%)	1 (2.7%)	**< 0.001**	**0.12 (0.20)**
0.5	37 (31.1%)	33 (29.2%)	4 (10.5%)	8 (21.6%)		
1.0	35 (29.4%)	40 (35.4%)	13 (34.2%)	10 (27%)		
1.5	20 (16.8%)	14 (12.4%)	7 (18.4%)	11 (29.7%)		
2.0	14 (11.8%)	15 (13.3%)	7 (18.4%)	4 (10.8%)		
2.5	2 (1.7%)	2 (1.8%)	1 (2.6%)	2 (5.4%)		
3.0	0	0	2 (5.3%)	1 (2.7%)		
mean score	**0.98**	**1.00**	**1.26**	**1.26**		

AD = Active dual pouch; AG = active topical gel; PD = Placebo dual pouch; and PG = placebo topical gel.

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Table A2.6: Comparison of Patient's Global Improvement Evaluation and Treatment Acceptability: Study #9709

	Treatment				Comparison[1]	
Variable	**AD (n=119)**	**AG (n=113)**	**PD (n=38)**	**PG (n=37)**	**AD vs. PD (p-value)**	**L.R. of 97.5% CI for (AD–AG) and –20% of reference mean**
Patient's Global Eval.						
N/A (No data)	6 (5%)	7 (6.2%)	5 (13.2%)	1 (2.7%)	< 0.001	–0.19 (–0.42)
0 (worse/no change)	2 (1.7%)	8 (7.1%)	7 (18.4%)	8 (21.6%)		
1 (somewhat better)	26 (21.8%)	17 (15%)	10 (26.3%)	7 (18.9%)		
2 (better)	38 (31.9%)	34 (30.1%)	12 (31.6%)	16 (43.2%)		
3 (much better)	47 (39.5%)	47 (41.6%)	4 (10.5%)	5 (13.5%)		
Subjects who rated improvement '*somewhat better*' and above	111/113 (98.2%)	98/106 (92.5%)	26/33 (78.8%)	28/36 (77.8%)	< 0.001	0.1%
Treatment Acceptability	99/113	91/106	22/33	26/36	0.005	–7.5%
Yes	(87.6%)	(85.8%)	(66.7%)	(72.2%)		

AD = active dual pouch; AG = active topical gel; PD = placebo dual pouch; PG = placebo topical gel.
[1]Analysis is based on the data provided on the final visit.

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Table A2.7: Efficacy Analyses in Pediatric vs. Adult Groups: Study #9709

Efficacy Variables	Pediatric (13 ≤ age ≤ 17) (n=157)					Adult (age > 17) (n=150)				
	AD (n=64)	AG (n=57)	PD (n=19)	PG (n=17)	p-value [1]	AD (n=55)	AG (n=56)	PD (n=19)	PG (n=20)	p-value [1]
% reduction in lesions										
Comedone	36.7%	43.6%	15.1%	12.6%	0.012	56.6%	41.9%	33.6%	26.7%	0.001
Inflammatory	41.8%	43.9%	0.3%	17.4%	< 0.001	57.6%	47.0%	33.2%	36.2%	0.003
Total	40.2%	44.0%	10.9%	18.1%	< 0.001	57.3%	43.6%	33.4%	32.4%	< 0.001
At least 80% reduction in lesions										
Comedone	9 (14%)	7 (12%)	0	0	0.086	14 (25%)	14 (25%)	1 (5%)	0	0.029
Inflammatory	11 (17%)	11 (19%)	0	0	0.062	20 (36%)	16 (29%)	2 (11%)	2 (10%)	0.012
Total	4 (6%)	8 (14%)	0	0	0.281	13 (24%)	11 (20%)	1 (5%)	0	0.039
Treatment success	13 (20%)	11 (19%)	0	0	0.029	20 (36%)	19 (34%)	1 (5%)	4 (20%)	0.009
Physician's acne severity score at Week8	1.36	1.25	1.82	1.91	0.001	0.95	1.05	1.39	1.45	0.007
facial oiliness score at Week 8	1.11	1.04	1.32	1.41	0.087	0.83	0.95	1.21	1.13	< 0.001
Patient's rating of improvement as *'somewhat better* +	61/63 (96.8%)	51/55 (92.7%)	11/16 (68.8%)	14/17 (82.4%)	< 0.001	50/50 (100%)	47/51 (92.2%)	15/17 (88.2%)	14/19 (73.7%)	0.017
Treatment acceptability Yes	53/63 (84.1%)	46/55 (83.6%)	10/16 (62.5%)	12/17 (70.6%)	0.068	46/50 (92%)	45/51 (88.2%)	12/17 (70.6%)	14/19 (73.7%)	0.016

AD = active dual pouch; AG = active gel; PD = placebo dual pouch; PG = placebo gel
[1]p-value listed is the comparison of AD vs. PD.

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Table A2.8: Efficacy Analyses in Female vs. Male Groups: Study #9709

Efficacy Variables	Female (n=157)					Male (n=150)				
	AD (n=62)	AG (n=53)	PD (n=21)	PG (n=21)	p-value [1]	AD (n=57)	AG (n=60)	PD (n=17)	PG (n=16)	p-value [1]
% reduction in lesions										
Comedone	56.5%	52.8%	29.1%	28.7%	0.003	34.3%	33.9%	18.5%	9.2%	0.091
Inflammatory	57.3%	48.7%	13.9%	36.9%	< 0.001	40.2%	42.5%	20.2%	15.3%	0.010
Total	57.1%	51.3%	23.3%	33.7%	< 0.001	38.4%	37.1%	20.7%	15.5%	0.064
At least 80% reduction in lesions										
Comedone	18 (29%)	16 (30%)	1 (5%)	0	0.029	5 (9%)	5 (8%)	0	0	0.338
Inflammatory	23 (37%)	16 (30%)	2 (10%)	2 (10%)	0.033	8 (14 %)	11 (18%)	0	0	0.134
Total	15 (24%)	14 (26%)	1 (5%)	0	0.078	2 (4%)	5 (8%)	0	0	0.529
Treatment success	20 (32%)	16 (30%)	1 (5%)	4 (19%)	0.017	13 (23%)	14 (23%)	0	0	0.070
Physician's acne severity score at Week8	1.04	1.07	1.57	1.43	0.001	1.32	1.23	1.65	1.97	0.019
facial oiliness score at Week 8	0.84	0.92	1.29	1.10	< 0.001	1.13	1.07	1.24	1.47	0.269
Patient's rating of improvement as *'somewhat better +'*	59/59 (100%)	46/50 (92%)	13/18 (72.2%)	16/21 (76.2%)	< 0.001	52/54 (96.3%)	52/56 (92.9%)	13/15 (86.7%)	12/15 (80%)	0.109
Treatment acceptability Yes	55/59 (93.2%)	44/50 (88%)	9/18 (50%)	16/21 (76.2%)	< 0.001	44/54 (81.5%)	47/56 (83.9%)	13/15 (86.7%)	10/15 (66.7%)	0.595

AD = active dual pouch; AG = active gel; PD = placebo dual pouch; PG = placebo gel

[1]p-value listed is the comparison of AD vs. PD.

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Table A2.9: Efficacy Analyses in Race Groups: Study #9709

Efficacy Variables	Caucasian (n=212)					Black (n=23)				Others (n=72)			
	AD (n=82)	AG (n=76)	PD (n=28)	PG (n=26)	p-value[1]	AD (n=10)	AG (n=9)	PD (n=2)	PG (n=2)	AD (n=27)	AG (n=28)	PD (n=8)	PG (n=9)
% reduction in lesions													
Comedone	50.6%	43.7%	19.5%	16.2%	< 0.001	16.3%	36.4%	31.1%	-23.5%	42.4%	42.3%	39.9%	41.5%
Inflammatory	50.3%	43.5%	11.3%	22.2%	< 0.001	47.1%	48.4%	37.5%	33.3%	46.1%	49.8%	30.5%	41.9%
Total	51.6%	43.9%	16.8%	21.6%	< 0.001	31.8%	37.8%	33.3%	8.3%	43.6%	45.3%	38.1%	41.8%
At least 80% reduction in lesions													
Comedone	21 (26%)	17 (22%)	1 (4%)	0	0.014	2 (20%)	0	0	0	0	4 (14%)	0	0
Inflammatory	25 (30%)	22 (29%)	2 (7%)	1 (4%)	0.014	2 (20%)	2 (22%)	0	0	4 (15%)	3 (11%)	0	1 (11%)
Total	16 (20%)	15 (20%)	1 (4%)	0	0.051	1 (10%)	0	0	0	0	4 (14%)	0	0
Treatment success	28 (34%)	19 (25%)	1 (4%)	1 (4%)	0.002	2 (20%)	1 (11%)	0	0	3 (11%)	10 (36%)	0	3 (33%)
Physician's acne severity score at Week8	1.18	1.21	1.70	1.79	< 0.001	1.20	1.11	2.00	2.25	1.13	1.02	1.19	1.17
Facial oiliness score at Week8	0.98	1.07	1.45	1.38	< 0.001	1.15	1.00	1.75	2.00	0.93	0.80	0.50	0.72
Patient's rating of improvement as *'somewhat better +'*	79/81 (97.5%)	67/72 (93.1%)	18/24 (75%)	20/25 (80%)	< 0.001	8/8 (100%)	9/9 (100%)	1/1 (100%)	0/2	24/24 (100%)	22/25 (88%)	7/8 (87.5%)	8/9 (88.9%)
Treatment acceptability Yes	69/81 (85.2%)	60/72 (83.3%)	15/24 (62.5%)	19/25 (76%)	0.020	8/8 (100%)	9/9 (100%)	0/1	0/2	22/24 (91.7%)	22/25 (88%)	7/8 (87.5%)	7/9 (77.8%)

AD = active dual pouch; AG = active gel; PD = placebo dual pouch; PG = placebo gel

[1]p-value listed is the comparison of AD vs. PD.

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Table A3.1: Comparison of Lesion Reduction at Week 2, 4, and 6: Study #9723

Assessment Week	Lesion Reduction	Treatment		p-value
		Active Dual (n=109)	Placebo Dual (n=108)	
		Comedone lesion		
Week 2	number reduction	7.99	5.36	0.141
	% reduction	18.9%	10.8%	0.013
Week 4	number reduction	11.33	8.62	0.110
	% reduction	27.1%	18.8%	0.018
Week 6	number reduction	13.23	11.56	0.420
	% reduction	31.3%	27.3%	0.480
		Inflammatory lesion		
Week 2	number reduction	10.30	6.57	0.002
	% reduction	36.9%	22.7%	< 0.001
Week 4	number reduction	13.51	7.92	< 0.001
	% reduction	46.7%	28.0%	< 0.001
Week 6	number reduction	15.35	8.41	< 0.001
	% reduction	53.4%	30.4%	< 0.001
		Total lesion (comedone + inflammatory)		
Week 2	number reduction	18.29	11.94	0.003
	% reduction	27.2%	16.5%	0.002
Week 4	number reduction	24.84	16.54	< 0.001
	% reduction	36.4%	23.0%	< 0.001
Week 6	number reduction	28.58	19.96	0.002
	% reduction	40.8%	29.0%	0.004

Table A3.2: Comparison of the Proportion of Subjects with at Least xx% Lesion Reduction at Week 8, where xx = 20 –100: Study #9723

	Comedone lesion			Inflammatory lesion			Total lesion		
xx%	AD (n=109)	PD (n=108)	p-value[1]	AD (n=109)	PD (n=108)	p-value[1]	AD (n=109)	PD (n=108)	p-value[1]
100	3 (2.8%)	4 (3.7%)	0.710	4 (3.7%)	2 (1.8%)	0.422	1 (0.9%)	0	0.302
90	7 (6.4%)	5 (4.6%)	0.534	13 (11.9%)	5 (4.6%)	0.048	5 (4.6%)	1 (0.9%)	0.088
80	16 (14.7%)	6 (5.6%)	0.025	34 (31.2%)	9 (8.3%)	< 0.001	17 (15.6%)	4 (3.7%)	0.002
70	24 (22%)	14 (13%)	0.071	52 (47.7%)	15 (13.9%)	< 0.001	24 (22%)	9 (8.3%)	0.004
60	32 (29.4%)	21 (19.4%)	0.087	63 (57.8%)	30 (27.8%)	< 0.001	36 (33%)	19 (17.6%)	0.008
50	45 (41.3%)	33 (30.6%)	0.100	72 (66.1%)	42 (38.9%)	< 0.001	55 (50.5%)	31 (28.7%)	< 0.001
40	52 (47.7%)	47 (43.5%)	0.522	79 (72.5%)	56 (51.8%)	0.002	72 (66.1%)	49 (45.4%)	0.002
30	64 (58.7%)	59 (54.6%)	0.517	86 (78.9%)	65 (60.2%)	0.003	80 (73.4%)	61 (56.5%)	0.009
20	76 (69.7%)	68 (63%)	0.276	91 (83.5%)	75 (69.4%)	0.015	87 (79.8%)	70 (64.8%)	0.012

AD = Active dual pouch; and PD = Placebo dual pouch.
[1] As a supporting analysis, comparison is intended to be informal as otherwise, one should address the multiplicity issue.

Table A3.3: Treatment Success at Week 2, 4, and 6: Study #9723

	Treatment		
Assessment Week	Active Dual (n=109)	Placebo Dual (n=108)	p-value
Week 2	6 (5.5%)	1 (0.9%)	0.058
Week 4	18 (16.5%)	5 (4.6%)	0.005
Week 6	25 (22.9%)	11 (10.2%)	0.011

Table A3.4: Comparison of Physician's Global Acne Severity Scores: Study #9723

	Global Acne Severity Score Distribution at Assessment Week							
	Week 2		Week 4		Week 6		Week 8	
Global score	AD (n=109)	PD (n=108)	AD (n=109)	PD (n=108)	AD (n=109)	PD (n=108)	AD (n=109)	PD (n=108)
0	0	0	0	0	0	0	2 (1.8%)	0
0.5	6 (5.5%)	1 (1%)	18 (16.5%)	5 (4.6%)	25 (22.9%)	11 (10.2%)	37 (33.9%)	13 (12%)
1.0	28 (25.7%)	14 (13%)	27 (24.8%)	22 (20.4%)	36 (33.1%)	21 (19.4%)	27 (24.8%)	25 (23.1%)
1.5	29 (26.6%)	33 (31%)	32 (29.3%)	29 (26.6%)	19 (17.4%)	29 (26.8%)	21 (19.3%)	27 (25%)
2.0	29 (26.6%)	37 (34%)	23 (21.1%)	30 (27.5%)	18 (16.5%)	24 (22.2%)	16 (14.7%)	22 (20.4%)
2.5	15 (13.8%)	14 (13%)	7 (6.4%)	16 (14.7%)	8 (7.3%)	18 (16.7%)	5 (4.6%)	13 (12%)
3.0	2 (2.8%)	8 (7%)	2 (2.8%)	6 (5.5%)	3 (2.7%)	5 (4.6%)	1 (1%)	8 (7.4%)
3.5	0	1 (1%)	0	0	0	0	0	0
mean score	**1.61**	**1.86**	**1.41**	**1.72**	**1.30**	**1.65**	**1.14**	**1.60**
p-value	0.003		< 0.001		< 0.001		< 0.001	

AD = Active dual pouch; and PD = Placebo dual pouch.

Table A3.5: Comparison of Facial Oiliness Scores: Study #9723

	Facial Oiliness Score Distribution at Assessment Week							
	Week 2		Week 4		Week 6		Week 8	
Oiliness score	AD (n=109)	PD (n=108)	AD (n=109)	PD (n=108)	AD (n=109)	PD (n=108)	AD (n=109)	PD (n=108)
0	20 (18.3%)	13 (12%)	22 (20.2%)	15 (13.9%)	30 (27.5%)	22 (20.4%)	40 (36.7%)	22 (20.4%)
0.5	13 (11.9%)	6 (5.6%)	23 (21.1%)	12 (11.1%)	23 (21.1%)	20 (18.5%)	25 (22.9%)	35 (32.4%)
1.0	38 (34.9%)	35 (32.4%)	36 (33%)	42 (38.9%)	27 (24.8%)	33 (30.5%)	24 (22%)	23 (21.3%)
1.5	23 (21.1%)	29 (26.8%)	19 (17.4%)	22 (20.4%)	16 (14.7%)	18 (16.7%)	12 (11.1%)	14 (13%)
2.0	14 (12.8%)	19 (17.6%)	8 (7.3%)	13 (12%)	11 (10.1%)	11 (10.2%)	7 (6.5%)	11 (10.2%)
2.5	1 (0.9%)	5 (4.6%)	1 (0.9%)	4 (3.7%)	2 (1.8%)	3 (2.8%)	1 (0.9%)	3 (2.8%)
3.0	0	1 (0.9%)	0	0	0	1 (0.9%)	0	0
mean score	**1.00**	**1.25**	**0.87**	**1.08**	**0.82**	**0.95**	**0.65**	**0.84**
p-value	0.018		0.036		0.388		0.062	

AD = Active dual pouch; and PD = Placebo dual pouch.

Table A3.6: Comparison of Patient's Global Improvement Evaluation and Treatment Acceptability: Study #9723

Variable	AD (n=109)	PD (n=108)	p-value [1]
Patient's Global Eval.			
N/A (No data)	10 (9.2%)	9 (8.3%)	0.002
0 (worse/no change)	4 (3.7%)	15 (13.9%)	
1 (somewhat better)	25 (22.9%)	29 (26.9%)	
2 (better)	35 (32.1%)	36 (33.3%)	
3 (much better)	35 (32.1%)	19 (17.6%)	
Subjects who rated improvement *'somewhat better'* and above	95/99 (96%)	84/99 (85%)	0.010
Treatment Acceptability			
Yes	87/99 (87.9%)	71/99 (71.7%)	0.005

AD = active dual pouch; PD = placebo dual pouch

[1] Analysis is based on the data provided on the final visit.

Table A3.7: Efficacy Analyses in Pediatric vs. Adult Groups: Study #9723

Efficacy variables	Pediatric (13<=age <= 17) (n=133)			Adult (age > 17) (n=84)		
	AD (n=65)	PD (n=68)	p-value	AD (n=44)	PD (n=40)	p-value
% reduction in lesions						
Comedone	31.9%	27.7%	0.381	42.6%	32.8%	0.482
Inflammatory	55.7%	33.7%	< 0.001	59.4%	34.8%	0.004
Total	42.3%	30.4%	0.006	49.7%	33.2%	0.056
At least 80% reduction in lesions						
Comedone	7 (11%)	3 (4%)	0.133	9 (20%)	3 (8%)	0.146
Inflammatory	16 (25%)	5 (7%)	0.004	18 (41%)	4 (10%)	0.002
Total	6 (9%)	2 (3%)	0.077	11 (25%)	2 (5%)	0.029
Treatment success	21 (32%)	5 (7%)	< 0.001	18 (41%)	8 (20%)	0.040
physician's global acne severity score at Week8	1.17	1.63	<0.001	1.10	1.54	0.050
facial oiliness score at Week8	0.66	0.92	0.043	0.64	0.71	0.689
Patient's rating of improvement						
(N/A)	5 (8%)	6 (9%)	0.069	5 (11%)	3 (8%)	0.409
0 (worse/no change)	1 (2%)	9 (13%)		3 (7%)	6 (15%)	
1 (somewhat better)	17 (26%)	20 (29%)		8 (18%)	9 (23%)	
2 (better)	19 (29%)	20 (29%)		16 (36%)	16 (40%)	
3 (much better)	23 (35%)	13 (19%)		12 (27%)	6 (15%)	
Patient's rating of improvement as '*somewhat better and above*'	59/60 (98%)	53/62 (85%)	0.013	36/39 (92%)	31/37 (84%)	0.292
Patient's rating of treatment acceptability Yes	54/60 (90%)	44/62 (71%)	0.011	33/39 (85%)	27/37 (73%)	0.134

AD = active dual pouch; PD = placebo dual pouch

Table A3.8: Efficacy Analyses in Female vs. Male Groups: Study #9723

Efficacy Variables	Female (n=109)			Male (n=108)		
	AD (n=56)	PD (n=53)	p-value	AD (n=53)	PD (n=55)	p-value
% reduction in lesions						
Comedone	44.9%	33.3%	0.162	27.0%	26.0%	0.907
Inflammatory	64.3%	39.6%	< 0.001	49.7%	28.9%	< 0.001
Total	53.0%	36.4%	0.008	37.1%	26.6%	0.066
At least 80% reduction in lesions						
Comedone	9 (16%)	3 (6 %)	0.057	7 (13%)	3 (5%)	0.214
Inflammatory	25 (45%)	6 (11%)	< 0.001	9 (17%)	3 (5%)	0.085
Total	13 (23%)	2 (4%)	< 0.001	4 (8%)	2 (4%)	0.582
Treatment success	27 (48%)	8 (15%)	< 0.001	12 (23%)	5 (9%)	0.044
physician's global acne severity score at Week8	0.92	1.48	< 0.001	1.38	1.71	0.003
facial oiliness score at Week8	0.63	0.83	0.356	0.68	0.85	0.182
Patient's rating of improvement						
(N/A)	4 (7%)	5 (9%)	0.208	6 (11 %)	4 (7%)	0.145
0 (worse/no change)	2 (4%)	7 (13%)		2 (4%)	8 (15%)	
1 (somewhat better)	12 (21%)	13 (25%)		13 (25%)	16 (29%)	
2 (better)	16 (29%)	18 (34%)		19 (36%)	18 (33%)	
3 (much better)	22 (39%)	10 (19%)		13 (25%)	9 (16%)	
Patient's rating of improvement as *'somewhat better and above'*	50/52 (96%)	41/48 (85%)	0.101	45/47 (96%)	43/51 (84%)	0.037
Patient's rating of treatment acceptability Yes	45/52 (86%)	33/48 (69%)	0.039	42/47 (89%)	38/51 (75%)	0.036

AD = active dual pouch; PD = placebo dual pouch

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Table A3.9: Efficacy Analyses in Race Groups: Study #9723

Efficacy Variables	Caucasian n=170			Black n=30		Others n=17	
	AD (n=91)	PD (n=79)	p-value	AD (n=12)	PD (n=18)	AD (n=6)	PD (n=11)
% reduction in lesions							
Comedone	37.3%	27.9%	0.109	22.5%	38.4%	45.9%	27.0%
Inflammatory	58.7%	33.6%	< 0.001	40.1%	37.1%	69.5%	33.2%
Total	46.3%	29.7%	< 0.001	31.6%	38.2%	56.5%	32.6%
At least 80% reduction in lesions							
Comedone	15 (16%)	3 (4%)	0.009	1 (8%)	2 (11%)	0	1 (9%)
Inflammatory	29 (32%)	4 (5%)	< 0.001	3 (25%)	5 (28%)	2 (33%)	0
Total	16 (18%)	2 (3%)	0.002	1 (8%)	2 (11%)	0	0
Treatment success	34 (37%)	9 (11%)	< 0.001	2 (17%)	3 (17%)	3 (50%)	1 (9%)
physician's global acne severity score at Week8	1.10	1.63	< 0.001	1.50	1.39	1.00	1.68
facial oiliness score at Week8	0.59	0.82	0.015	1.13	1.08	0.67	0.59
Patient's rating of improvement			0.111				
(N/A)	6 (7%)	5 (6%)		4 (33%)	3 (17%)	0	1 (9%)
0 (worse/no change)	4 (4%)	11 (14%)		0	3 (17%)	0	1 (9%)
1 (somewhat better)	20 (22%)	22 (28%)		3 (25%)	6 (33%)	2 (33%)	1 (9%)
2 (better)	30 (33%)	25 (32%)		3 (25%)	5 (28%)	2 (33%)	6 (55%)
3 (much better)	31 (34%)	16 (20%)		2 (17%)	1 (6%)	2 (33%)	2 (18%)
Patient's rating of improvement as '*somewhat better and above*'	81/85 (95.3%)	63/74 (85.1%)	0.039	8/8 (100%)	12/15 (80%)	6/6 (100%)	9/10 (90%)
Patient's rating of treatment acceptability Yes	77/85 (90.6%)	51/74 (68.9%)	< 0.001	7/8 (87.5%)	11/15 (73.3%)	3/6 (50%)	9/10 (90%)

AD = active dual pouch; PD = placebo dual pouch

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