U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number:	20-723 / SE8-020
Drug Name:	Aldara (imiquimod)
Indication(s):	Molluscum Contagiosum
Applicant:	3M
Dates:	Submitted: 9/22/06 PDUFA: 3/22/07
Review Priority:	Priority review
Biometrics Division:	Division of Biometrics III
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Keywords: pediatric exclusivity

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1 Executive Summary

1.1 Conclusions and Recommendations

Studies 1494 and 1495 failed to demonstrate the efficacy of Aldara (imiquimod) in the treatment of molluscum contagiosum. The complete clearance rate on the Aldara arm was worse than the vehicle arm in both studies. Subjects treated lesions three times a week for 16 weeks. The complete clearance rate at Week 18 was 24% on the Aldara arm in both studies and was 2-4% higher on the vehicle arm in each study (26% and 28%). The studies were submitted to the Agency to fulfill a Pediatric Written Request. The studies were conducted according to the terms of the Written Request and Pediatric Exclusivity was granted by the Agency on December 13, 2006. The sponsor is not pursuing efficacy claims regarding molluscum contagiosum.

1.2 Brief Overview of Clinical Studies

The key study design features for Studies 1494 and 1495 were laid out in a Written Request initially issued on December 28, 2001 and with final amendment on May 5, 2006. The sponsor's studies met all of the terms of the Written Request. The studies enrolled subjects aged 2 – 12 with at least two molluscum lesions. The subjects were randomized to apply either Aldara or vehicle three times per week for 16 weeks. The primary efficacy endpoint was the complete clearance of all lesions at Week 18 (two weeks post-treatment). Study 1494 enrolled 217 Aldara and 106 vehicle subjects and Study 1495 enrolled 253 Aldara and 126 vehicle subjects. Both studies were conducted in the United States.

1.3 Statistical Issues and Findings

Neither Study 1494 nor 1495 demonstrated statistical significance for Aldara versus vehicle in the treatment of molluscum contagiosum. In fact, in both studies vehicle had a higher success rate than Aldara. The secondary endpoints also did not detect any differences between Aldara and vehicle. None of the results were statistically significant and vehicle sometimes had higher observed success rates than Aldara. The secondary endpoints included partial clearance (at least 50% reduction in lesions), median percent reduction in lesions, time to clearance, and recurrence at Week 28. The sponsor is not pursuing efficacy claims for molluscum contagiosum.

2 Introduction

2.1 Overview

Aldara (imiquimod) was first approved in the U.S in 1997 and is approved for external genital warts, actinic keratosis, and superficial basal cell carcinoma in certain populations. Imiquimod is an immune response modifier. Aldara has been a product of 3M Pharmaceuticals, but during the review of this supplement, the ownership of the product was transferred to Graceway Pharmaceuticals. Aldara is used off-label in molluscum contagiosum (MC) and the studies based on the Pediatric Written Request were designed to elucidate the treatment effect in MC in pediatric subjects. The Pediatric Written Request was first issued on December 28, 2001 and the final amended version

was issued on May 5, 2006. The studies were conducted from 2004 to 2005. All study centers were in the United States. The studies conducted under the Written Request are listed in Table 1. The Pediatric Exclusivity Board determined that the conducted studies met the terms of the Written Request and Pediatric Exclusivity was granted on December 13, 2006. This review will evaluate the two safety and efficacy studies (1494 and 1495).

Table 1 – Clinical Study Program for Molluscum Contagiosum

Study	Purpose	Number of Subjects
IMIQ-1494	Efficacy and Safety	217 Aldara, 106 Vehicle
IMIQ-1495	Efficacy and Safety	253 Aldara, 126 Vehicle
IMIQ-1498	Pharmacokinetics	22 Aldara

2.2 Data Sources

This reviewer evaluated the sponsor's study reports as well as the proposed labeling. The study reports were submitted electronically. The datasets used in this review are archived at \\CDSESUB1\N20723\N_000\2006-11-08\crt\datasets. Note that the datasets for this submission are located in the N_000 folder rather than the S_020 folder which contains the other electronic files for this submission.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study Design

Studies 1494 and 1495 were randomized, vehicle-controlled studies in subjects 2 – 12 years old with at least two molluscum contagiosum lesions. Subjects treated their lesions three times per week for up to 16 weeks. Subjects were evaluated at baseline and Weeks 2, 4, 8, 12, 16, 18, and 28. The primary efficacy endpoint was complete clearance of lesions at Week 18. The secondary endpoint was partial clearance (≥50% of lesions) at Week 18. The details of the study design for Studies 1494 and 1495 were laid out in the Pediatric Written Request, including requirements that at least half of the subjects were to be under 6 years (at least 20% under 4 years), at least half of the subjects were to have at least 5 lesions, and at least 25 imiquimod-treated subjects in the two studies were to have periocular lesions. The two studies together were to enroll a minimum of 300 imiquimod-treated subjects. In addition to lesion counts, investigators actively assessed local skin reactions, including erythema, edema, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting.

The ITT population was defined as all randomized subjects. The per protocol population included subjects who did not have a major protocol violation, had a Week 18 lesion assessment between weeks 16 and 20, and applied at least two-thirds of the required doses. Clearance rates were analyzed with Cochran-Mantel-Haenszel tests stratified on center.

3.1.2 Subject Disposition

Study 1494 enrolled 217 imiquimod and 106 vehicle subjects and Study 1495 enrolled 253 imiquimod and 126 vehicle subjects. The most common reasons for discontinuation were loss to follow-up and personal reasons. The discontinuation rates were similar on both the imiquimod and vehicle arms, with a higher rate of vehicle arm discontinuations than imiquimod in Study 1494, but comparable discontinuation rates in Study 1495. The discontinuation reasons and rates for the two studies are presented in Table 2 and Table 3.

Table 2 – Subjects Discontinuing during the Treatment Period (Study 1494)

Primary Reason for Discontinuation	Imiquimod (n=217)	Vehicle (n=106)
Adverse Event	2 (0.9%)	1 (0.9%)
Lost to Follow-up	23 (10.6%)	12 (11.3%)
Personal	5 (2.3%)	5 (4.7%)
Lack of Therapeutic Effect	1 (0.5%)	2 (1.9%)
Other	1 (0.5%)	1 (0.9%)
Total	32 (14.7%)	21 (19.8%)

Source: molluscumcontagiosum.pdf pg. 82

Table 3 - Subjects Discontinuing during the Treatment Period (Study 1495)

Primary Reason for Discontinuation	Imiquimod (n=253)	Vehicle (n=126)
Adverse Event	3 (1.2%)	1 (0.8%)
Lost to Follow-up	15 (5.9%)	6 (4.8%)
Personal	6 (2.4%)	3 (2.4%)
Lack of Therapeutic Effect	5 (2.0%)	5 (4.0%)
Other	2 (0.8%)	1 (0.8%)
Local Skin Reaction/Sign	1 (0.4%)	0 (0.0%)
Total	32 (12.6%)	16 (12.7%)

Source: molluscumcontagiosum.pdf pg. 7587

3.1.3 Baseline and Demographic Data

Both studies were relatively balanced across treatment arms for demographic variables. About equal numbers of male and female subjects were enrolled and the subjects were predominately white and non-Hispanic. The mean number of baseline lesions was 28 (median 17) in Study 1494 and 22 (median 15) in Study 1495. The baseline and demographic data are presented in Table 4 and Table 5.

Table 4 – Baseline and Demographic Data (Study 1494)

Variable Description	Statistic/ Level	Imiquimod (n=217)	Vehicle (n=106)
Sex	Female	109 (50.2%)	51 (48.1%)
	Male	108 (49.8%)	55 (51.9%)
Age	Mean	5.2	5.1
	Range	2 – 12	2 – 12
Race	White	203 (93.5%)	102 (96.2%)
	Black/African American	11 (5.1%)	4 (3.8%)
	Asian	1 (0.5%)	0 (0.0%)
	Native Hawaiian/ Other Pacific Islander	2 (0.9%)	0 (0.0%)
Ethnicity	Unknown	1 (0.5%)	0 (0.0%)
	Not Hispanic / Latino	187 (86.2%)	93 (87.7%)
	Hispanic / Latino	29 (13.4%)	13 (12.3%)
Periocular Lesions	Yes	14 (6.5%)	12 (11.3%)
	No	203 (93.5%)	94 (88.7%)
Baseline Lesions	<5	13 (6.0%)	9 (8.5%)
	5 - 15	76 (35.0%)	41 (38.7%)
	16 - 30	66 (30.4%)	29 (27.4%)
	31 - 50	29 (13.4%)	15 (14.2%)
	>50	33 (15.2%)	12 (11.3%)
	Mean	29.5	24.0
	Range	2 – 462	2 – 160

Source: molluscumcontagiosum.pdf pg. 87 and 93

Table 5 – Baseline and Demographic Data (Study 1495)

Variable Description	Statistic/Level	Imiquimod (n=253)	Vehicle (n=126)
Sex	Female	132 (52.2%)	77 (61.1%)
	Male	121 (47.8%)	49 (38.9%)
Age	Mean	5.5	5.9
	Range	2 – 12	2 – 12
Race	White	241 (95.3%)	119 (94.4%)
	Black/African American	6 (2.4%)	6 (4.8%)
	American Indian/Alaska Native	1 (0.4%)	0 (0.0%)
	Asian	3 (1.2%)	1 (0.8%)
	Native Hawaiian/Other/ Pacific Islander	2 (0.8%)	0 (0.0%)
Ethnicity	Not Hispanic/Latino	227 (89.7%)	110 (87.3%)
	Hispanic/Latino	26 (10.3%)	16 (12.7%)
Periocular Lesions	Yes	22 (8.7%)	11 (8.7%)
	No	231 (91.3%)	115 (91.3%)
Baseline Lesions	<5	32 (12.6%)	19 (15.1%)
	5 - 15	94 (37.2%)	52 (41.3%)
	16 - 30	65 (25.7%)	26 (20.6%)
	31 - 50	38 (15.0%)	17 (13.5%)
	>50	24 (9.5%)	12 (9.5%)
	Mean	22.9	21.9
	Range	2 - 148	2 - 119

Source: molluscumcontagiosum.pdf pg. 7592 and 7599

3.1.4 Primary Efficacy Endpoint

Both studies failed to demonstrate the superiority of imiquimod over vehicle in the complete clearance of lesions at Week 18. In fact the observed complete clearance rate on the imiquimod arm in each study was lower than on the vehicle arm. The results from the ITT and per protocol populations are similar, except that in the per protocol population, the point estimate for the complete clearance rate on the imiquimod arm is numerically higher than the estimate for vehicle in Study 1494. The primary efficacy results are presented in Table 6 (ITT) and Table 7 (PP). The complete clearance rates were analyzed with a Cochran-Mantel-Haenszel test stratified on pooled center. Centers with fewer than 12 subjects were pooled with the center with the next higher center number within their geographic region (northeast, southeast, northwest, or southwest). Note that the p-values for these analyses are two-sided p-values. Had the alternative hypothesis been set up as a one-sided hypothesis (H_1: $p_{imiq} > p_{veh}$ at α=0.025) rather than as a two-sided test (H_1: $p_{imiq} \neq p_{veh}$ at α=0.05) the p-values would have been 0.6681 in Study 1494 and 0.8185 in Study 1495, by calculating the area under the distribution curve to the right of the test statistic rather than twice the (left) tail area.

Table 6 – Complete Clearance Rate at Week 18 (ITT)

Study	Aldara	Vehicle	P-value
1494	24% (52/217)	26.4% (28/106)	0.6638
1495	23.7% (60/253)	27.8% (35/126)	0.3631

Source: molluscumcontagiosum.pdf pg. 278 and 7791

Table 7 – Complete Clearance Rate at Week 18 (PP)

Study	Aldara	Vehicle	P-value
1494	29.3% (43/147)	24.6% (15/61)	0.4006
1495	25.8% (42/163)	31.3% (26/83)	0.2324

Source: molluscumcontagiosum.pdf pg. 279 and 7792

3.1.5 Secondary Efficacy Analyses

The study protocols specified the secondary endpoints as change in lesion count from baseline to Week 18, partial clearance (at least 50% reduction in lesions from baseline to Week 18), time to complete clearance, and 'similar analyses at Week 28'. The statistical analysis plan clarified these endpoints as partial clearance at Week 18, median percent reduction in lesions at each visit, time to complete clearance, complete clearance by body site, recurrence at Week 28, and complete clearance at Week 28.

The partial clearance rates (at least 50% reduction in lesions from baseline to Week 18) are about 20-25% higher in each arm than the complete clearance rates. The partial

clearance rates also did not demonstrate statistical significance in either study ($p \geq 0.44$). Imiquimod had a slightly higher partial clearance rate than vehicle in one study, but the reverse was true in the other study. The partial clearance rates for the ITT population are presented in Table 8. Another secondary endpoint was the median percent reduction in lesions from baseline to Week 18. The sponsor did not assess statistical significance for this endpoint. Again imiquimod had slightly more favorable results in one study and vehicle in the other. The median percent reductions are also presented in Table 8. The results of the analyses by body region are presented in Section 4.2

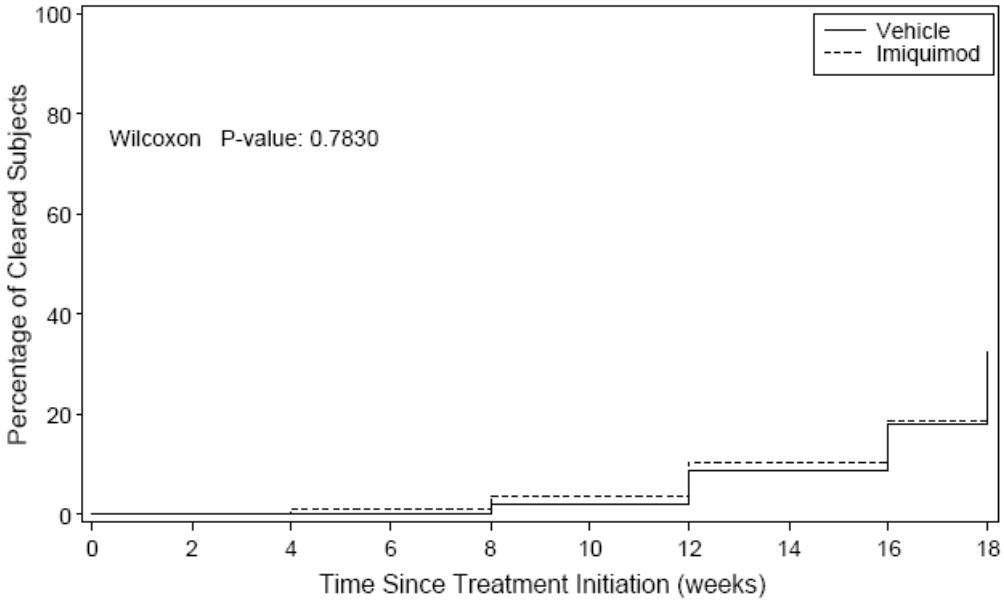
Table 8 – Secondary Endpoints at Week 18 (ITT)

	Study 1494		Study 1495	
	Imiquimod	**Vehicle**	**Imiquimod**	**Vehicle**
Partial Clearance Rate	49.8% (108/217)	45.3% (48/106)	47.8% (121/253)	50% (63/126)
Median % Reduction	48.1%	37.3%	41.7%	48.5%

Source: molluscumcontagiosum.pdf pg. 296, 328, 7809 and 7841.

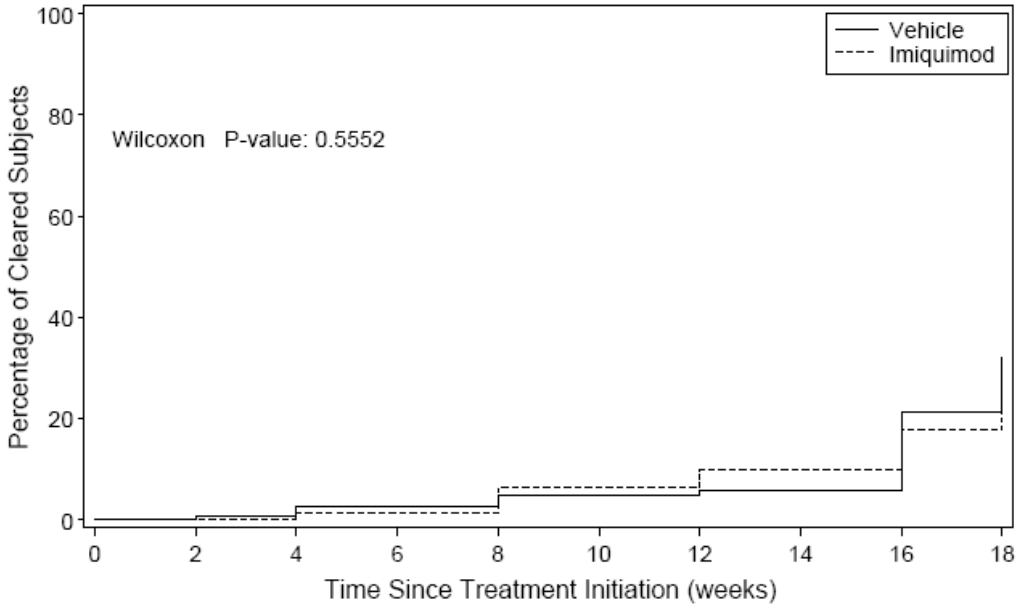
In addition, there were no significant differences between imiquimod and vehicle on the time to complete clearance. The Kaplan-Meier curves and p-values are presented in Figure 1 and Figure 2.

Figure 1 - Time to Clearance (Study 1494)



Source: molluscumcontagiosum.pdf pg. 119

Figure 2 – Time to Clearance (Study 1495)



Source: molluscumcontagiosum.pdf pg. 7625

At the Week 28 assessment, most of the subjects who had cleared by Week 18 remained clear (50/52 [96%] in Study 1494 and 53/60 [88%] in Study 1495). In addition, many subjects who had not cleared by the Week 18 visit were cleared by the Week 28 visit. In Study 1494, an additional 35 imiquimod subjects (16%) and 12 vehicle subjects (11%) were clear at Week 28 (excluding subjects who cleared after using alternate therapies). Similarly an additional 38 imiquimod (15%) and 14 vehicle subjects (11%) in Study 1495 were clear by Week 28 without using alternative therapies.

Table 9 – Lesion Assessment at Week 28 (ITT)

	Study 1494		Study 1495	
	Imiquimod N=217	**Vehicle N=106**	**Imiquimod N=253**	**Vehicle N=126**
Subj. clear at Wk 18	52 (24%)	28 (26%)	60 (24%)	35 (28%)
Subj. remaining clear at Wk 28	50 (23%)	27 (25%)	53 (21%)	32 (25%)
Subj. with recurrence at Wk 28	1 (<1%)	0 (0%)	3 (1%)	0 (0%)
No assessment at Wk 28	1 (<1%)	1 (1%)	4 (2%)	3 (2%)
Subj. not clear or with no assessment at Wk 18	165 (76%)	78 (74%)	193 (76%)	91 (72%)
Subj. clear at Wk 28	39 (18%)	16 (15%)	38 (15%)	17 (13%)
[Subj. with alt. therapy][1]	[4] (2%)	[4] (4%)	[0] (0%)	[3] (2%)
Subj. not clear at Wk 28	82 (38%)	36 (34%)	120 (47%)	54 (43%)
No Assessment at Wk 28	44 (20%)	26 (25%)	35 (14%)	20 (16%)

[1] Number of subjects included as cleared who received alternate therapy.
Source: molluscumcontagiosum.pdf pg 123 and 7629.

3.2 Evaluation of Safety

3.2.1 Local Skin Reactions

Six local skin reactions (erythema, edema, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting) were actively assessed on a 4-point scale at each visit. The most intense score for each category are tabulated in Table 10. For each category, the proportion of subjects with moderate or severe reactions was higher on imiquimod than vehicle in both studies. A significant proportion of imiquimod subjects had at least one report of severe erythema (32% in Study 1494 and 24% in Study 1495 versus 7% to 11% on vehicle).

Table 10 – Most Intense Local Skin Reaction during the Study

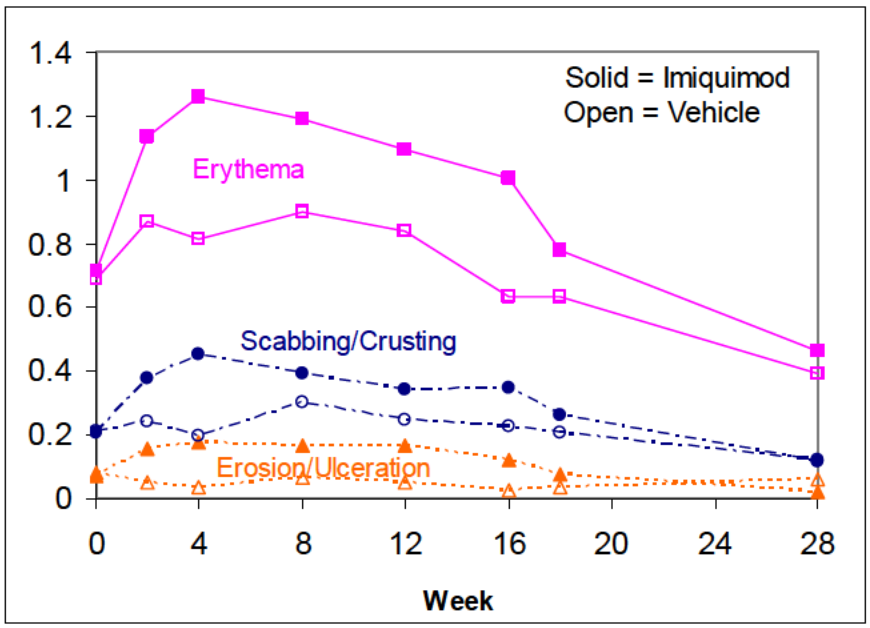
		Study 1494		Study 1495	
Type of Reaction	**Intensity**	**Imiquimod (n=211)**	**Vehicle (n=101)**	**Imiquimod (n=249)**	**Vehicle (n=122)**
Erythema	None	16 (7.6%)	13 (12.9%)	18 (7.2%)	15 (12.3%)
	Mild	43 (20.4%)	39 (38.6%)	47 (18.9%)	34 (27.9%)
	Moderate	84 (39.8%)	42 (41.6%)	124 (49.8%)	59 (48.4%)
	Severe	68 (32.2%)	7 (6.9%)	60 (24.1%)	14 (11.5%)
Edema	None	77 (36.5%)	51 (50.5%)	94 (37.8%)	53 (43.4%)
	Mild	59 (28.0%)	32 (31.7%)	64 (25.7%)	34 (27.9%)
	Moderate	55 (26.1%)	16 (15.8%)	73 (29.3%)	32 (26.2%)
	Severe	20 (9.5%)	2 (2.0%)	18 (7.2%)	3 (2.5%)
Erosion/Ulceration	None	131 (62.1%)	86 (85.1%)	179 (71.9%)	101 (82.8%)
	Mild	47 (22.3%)	10 (9.9%)	39 (15.7%)	17 (13.9%)
	Moderate	26 (12.3%)	5 (5.0%)	27 (10.8%)	4 (3.3%)
	Severe	7 (3.3%)	0 (0.0%)	4 (1.6%)	0 (0.0%)
Weeping/Exudate	None	169 (80.1%)	94 (93.1%)	220 (88.4%)	114 (93.4%)
	Mild	32 (15.2%)	7 (6.9%)	18 (7.2%)	6 (4.9%)
	Moderate	4 (1.9%)	0 (0.0%)	10 (4.0%)	2 (1.6%)
	Severe	6 (2.8%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Flaking/Scaling/Dryness	None	61 (28.9%)	47 (46.5%)	100 (40.2%)	66 (54.1%)
	Mild	67 (31.8%)	38 (37.6%)	66 (26.5%)	34 (27.9%)
	Moderate	68 (32.2%)	16 (15.8%)	74 (29.7%)	21 (17.2%)
	Severe	15 (7.1%)	0 (0.0%)	9 (3.6%)	1 (0.8%)
Scabbing/Crusting	None	73 (34.6%)	45 (44.6%)	85 (34.1%)	63 (51.6%)
	Mild	68 (32.2%)	39 (38.6%)	86 (34.5%)	35 (28.7%)
	Moderate	57 (27.0%)	17 (16.8%)	69 (27.7%)	22 (18.0%)
	Severe	13 (6.2%)	0 (0.0%)	9 (3.6%)	2 (1.6%)

Source: molluscumcontagiosum.pdf pg 143 and 7649.

The mean score for all local skin reactions was higher on imiquimod than vehicle throughout the 16-week treatment period (where 0=none, 1=mild, 2=moderate, 3=severe). Vehicle levels remained similar to the baseline values throughout the study. During the post-treatment period, the mean imiquimod score returned to a similar level as

the vehicle group. Figure 3 presents the mean score by visit for erythema, scabbing/crusting, and erosion ulceration for the two studies combined. The results for edema, weeping/exudate, and flaking/scaling/dryness are similar and not presented here.

Figure 3 – Mean Local Skin Reaction Score by Visit for Combined Studies



Source: Reviewer Analysis

3.2.2 Adverse Events

The proportion of subjects with at least one adverse event was similar on both the imiquimod and vehicle arms in both studies (69% imiquimod vs. 74% vehicle in Study 1494 and 66% imiquimod vs. 67% vehicle in Study 1495). However, the proportion of subjects with application site reactions, the most common adverse event, was higher on the imiquimod arms (36% imiquimod vs. 20% vehicle in Study 1494 and 32% vs. 25% in Study 1495). Table 11 displays the included terms for application site reactions observed in at least 2% of subjects. The most common application site reactions were erythema and irritation.

Table 11 – Included Terms for Application Site Reaction (>2% Incidence)

	Study 1494		Study 1495	
	Imiquimod (n=217)	**Vehicle (n=106)**	**Imiquimod (n=253)**	**Vehicle (n=126)**
Any Adverse Event	149 (68.7%)	78 (73.6%)	166 (65.6%)	84 (66.7%)
Application Site Reaction	77 (35.5%)	21 (19.8%)	80 (31.6%)	31 (24.6%)
Included terms (>2%)				
Bleeding at target site	7 (3.2%)	2 (1.9%)	3 (1.2%)	3 (2.4%)
Dryness at target site	8 (3.7%)	1 (0.9%)	5 (2.0%)	3 (2.4%)
Erythema at target site	36 (16.6%)	8 (7.5%)	21 (8.3%)	13 (10.3%)
Infection at target site	6 (2.8%)	2 (1.9%)	11 (4.3%)	4 (3.2%)
Irritation at target site	19 (8.8%)	2 (1.9%)	20 (7.9%)	6 (4.8%)
Itching at target site	19 (8.8%)	7 (6.6%)	8 (3.2%)	7 (5.6%)
Pain at target site	10 (4.6%)	3 (2.8%)	5 (2.0%)	1 (0.8%)
Rash at target site	8 (3.7%)	2 (1.9%)	15 (5.9%)	5 (4.0%)
Scabbing at target site	7 (3.2%)	4 (3.8%)	7 (2.8%)	1 (0.8%)
Soreness at target site	0 (0.0%)	0 (0.0%)	4 (1.6%)	3 (2.4%)
Swollen at target site	5 (2.3%)	5 (4.7%)	6 (2.4%)	0 (0.0%)

Source: molluscumcontagiosum.pdf pg 419 and 7927.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

The complete clearance rate did not vary substantially across sex, race, ethnicity, or age. The results in the individual subgroups are consistent with the overall findings of similar clearance rates for imiquimod and vehicle. Sex, race, ethnicity, and age subgroup results are presented in Table 12.

Table 12 – Complete Clearance Rate by Subgroup

		Study 1494		Study 1495	
Subgroup	**Level**	**Imiquimod**	**Vehicle**	**Imiquimod**	**Vehicle**
Sex	Female	22.0% (24/109)	29.4% (15/51)	24.2% (32/132)	29.9% (23/77)
	Male	25.9% (28/108)	23.6% (13/55)	23.1% (28/121)	24.5% (12/ 49)
Race	White	23.6% (48/203)	26.5% (27/102)	23.2% (56/241)	27.7% (33/119)
	Nonwhite	28.6% (4/14)	25.0% (1/4)	33.3% (4/12)	28.6% (2/7)
Ethnicity	Unknown	0.0% (0/1)	-- (0/0)	-- (0/0)	-- (0/0)
	Hispanic/ Latino	24.1% (7/29)	23.1% (3/13)	11.5% (3/26)	18.8% (3/16)
	Not Hispanic/ Latino	24.1% (45/187)	26.9% (25/93)	25.1% (57/227)	29.1% (32/110)
Age Group (years)	<4	19.4% (12/62)	12.9% (4/31)	22.6% (14/62)	19.2% (5/26)
	4 - 5	20.0% (12/60)	28.6% (10/35)	24.7% (21/85)	27.3% (9/33)
	6 - 7	25.5% (14/55)	38.1% (8/21)	14.9% (7/47)	25.0% (9/36)
	8 - 9	33.3% (10/30)	33.3% (4/12)	22.9% (8/35)	42.1% (8/19)
	>9	40.0% (4/10)	28.6% (2/7)	41.7% (10/24)	33.3% (4/12)

Source: molluscumcontagiosum.pdf pg. 103 and 7609

4.2 Other Special/Subgroup Populations

The sponsor also compiled clearance rates by other subgroups such as whether or not they had periocular lesions, atopic dermatitis, or baseline erythema, as well as by dosing compliance and duration of molluscum contagiosum. The sponsor also investigated clearance rates by baseline lesion count and by body site. These results are presented in Table 13, Table 14, and Table 15. Again, no obvious trends are observable in any of these subgroups.

Table 13 – Complete Clearance Rate by Subgroup

		Study 1494		Study 1495	
Subgroup	**Level**	**Imiquimod**	**Vehicle**	**Imiquimod**	**Vehicle**
Periocular Lesions	Yes	28.6% (4/14)	33.3% (4/12)	4.5% (1/22)	18.2% (2/11)
	No	23.6% (48/203)	25.5% (24/94)	25.5% (59/231)	28.7% (33/115)
Atopic Dermatitis	Yes	27.0% (10/37)	7.7% (1/13)	34.1% (15/44)	37.5% (9/24)
	No	23.3% (42/180)	29.0% (27/93)	21.5% (45/209)	25.5% (26/102)
Dosing Compliance	Unknown	0.0% (0/11)	0.0% (0/5)	0.0% (0/12)	0.0% (0/3)
	≥100%	17.5% (11/63)	29.0% (9/31)	24.7% (19/77)	30.4% (14/46)
	90 - <100%	30.9% (21/68)	19.4% (6/31)	19.1% (13/68)	20.0% (6/30)
	80 - <90%	28.1% (9/32)	46.2% (6/13)	30.8% (12/39)	50.0% (9/18)
	70 - <80%	35.7% (5/14)	37.5% (3/8)	25.0% (5/20)	27.3% (3/11)
	60 - <70%	50.0% (4/8)	66.7% (2/3)	47.1% (8/17)	40.0% (2/5)
	<60%	9.5% (2/21)	13.3% (2/15)	15.0% (3/20)	7.7% (1/13)
Baseline Erythema	Any	26.3% (30/114)	30.8% (16/52)	28.6% (40/140)	30.6% (19/62)
	None	21.4% (22/103)	22.2% (12/54)	17.7% (20/113)	25.0% (16/64)
MC Duration (months)	Unknown	25.0% (1/4)	0.0% (0/4)	0.0% (0/2)	100.0% (1/1)
	0 - <3	29.6% (16/54)	26.3% (5/19)	19.2% (14/73)	11.6% (5/43)
	3 - <6	17.0% (9/53)	26.9% (7/26)	28.3% (13/46)	29.2% (7/24)
	6 - <12	30.6% (19/62)	23.5% (8/34)	28.8% (21/73)	53.6% (15/28)
	≥12	15.9% (7/44)	34.8% (8/23)	20.3% (12/59)	23.3% (7/30)

Source: molluscumcontagiosum.pdf pg. 103 and 7609

Table 14 – Complete Clearance Rate by Baseline Count (Study 1494)

	Study 1494		Study 1495	
Baseline MC Lesion Count	**Imiquimod**	**Vehicle**	**Imiquimod**	**Vehicle**
≤15 MC Lesions	22.5% (20/89)	18.0% (9/50)	21.4% (27/126)	28.2% (20/71)
>15 MC Lesions	25.0% (32/128)	33.9% (19/56)	26.0% (33/127)	27.3% (15/55)

Source: molluscumcontagiosum.pdf pg. 104 and 7610

Table 15 – Complete Clearance Rate within Body Site at Week 18

	Study 1494		Study 1495	
Body Site	**Imiquimod**	**Vehicle**	**Imiquimod**	**Vehicle**
Anterior Trunk	42.5% (71/167)	35.5% (27/ 76)	43.0% (77/179)	46.7% (42/ 90)
Buttocks	54.4% (37/ 68)	41.0% (16/ 39)	51.9% (42/ 81)	67.7% (21/ 31)
Head	47.2% (25/ 53)	32.3% (10/ 31)	35.9% (28/ 78)	36.7% (11/ 30)
Left Lower Extremity	44.6% (58/130)	46.0% (29/ 63)	41.5% (61/147)	45.7% (32/ 70)
Left Upper Extremity	44.1% (56/127)	38.9% (21/ 54)	42.6% (49/115)	50.0% (26/ 52)
Neck	48.3% (28/ 58)	36.4% (12/ 33)	36.8% (25/ 68)	48.1% (13/ 27)
Periocular	40.0% (6/ 15)	50.0% (6/ 12)	33.3% (8/ 24)	50.0% (6/ 12)
Posterior Trunk	48.6% (52/107)	49.0% (24/ 49)	52.2% (47/ 90)	48.1% (26/ 54)
Right Lower Extremity	44.2% (57/129)	37.7% (23/ 61)	35.1% (53/151)	44.8% (30/ 67)
Right Upper Extremity	50.0% (54/108)	46.2% (18/ 39)	42.9% (60/140)	51.7% (31/ 60)

Note: The denominator is the number of subjects with a body site MC lesion count greater than 0 on or prior to the week 18 study visit. The numerator is the number of subjects with a body site MC lesion count greater than 0 before week 18 and a week 18 MC lesion assessment of 0 remaining in the body site.
Source: molluscumcontagiosum.pdf pg. 332 and 7845

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Both studies 1494 and 1495 failed to demonstrate the efficacy of imiquimod in the treatment of molluscum contagiosum. In each study the complete clearance rate was actually higher on vehicle than on imiquimod. Results for the secondary endpoints were consistent with the primary endpoint and also did not support efficacy. Results in the subgroups based on baseline and demographic information were consistent with the overall finding of no efficacy for imiquimod. These studies enrolled subjects age 2 to 12 who treated their lesions three times a week for 16 weeks. Although no efficacy benefits for imiquimod were seen, imiquimod subjects did experience more severe local skin reactions including erythema, edema, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting.

5.2 Conclusions and Recommendations

The complete clearance rates for imiquimod (24% in both studies) were lower than the complete clearance rates for vehicle (26% in Study 1494 and 28% in Study 1495) and efficacy was not demonstrated. Studies 1494 and 1495 met the criteria in the Pediatric Written Request and Pediatric Exclusivity was granted on December 13, 2006. Because the sponsor has been granted exclusivity based on these studies, this reviewer recommends including the results of the studies in labeling even though they failed to demonstrate efficacy.

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Date: February 15, 2007

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