CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201153Orig1s000

STATISTICAL REVIEW(S)

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:	201153 / 000 (Reference to : 22483)
Drug Name:	Zyclara (imiquimod) 3.75%
Indication(s):	External Genital Warts
Applicant:	Graceway
Dates:	Submitted: 2/8/2010 PDUFA: 12/8/2010
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III
Statistics Reviewer:	Kathleen Fritsch, PhD
Concurring Reviewer:	Mohamed Alosh, PhD
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Keywords: external genital warts, gender subgroups, missing data

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1 Executive Summary

1.1 Conclusions and Recommendations

Zyclara (imiquimod) cream 3.75% applied once daily for up to 8 weeks was superior to vehicle in the treatment of external genital warts in two studies ($p \leq 0.001$, statistically significant after adjusting for multiplicity due to two dose groups). The studies also evaluated imiquimod cream 2.5% which was only superior to vehicle in one of the two studies. The studies enrolled subjects at least 12 years of age with 2-30 genital/perianal warts with a total wart area of at least 10 mm^2. The primary efficacy endpoint was complete clearance of all warts (baseline and new) on or before Week 16 as determined by the investigator. Subjects stopped treatment when complete clearance was achieved. Approximately 28% of imiquimod 3.75% subjects vs. 9% of vehicle subjects achieved complete clearance. See Table 1.

Table 1 - Complete Clearance Rates at End of Study

Study	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
0801	53/195 (27%) 0.001*	34/178 (19%) 0.065	10/97 (10%)
0805	60/204 (29%) <0.001*	50/202 (25%) 0.001*	9/105 (9%)

P-values (vs. vehicle) are from Cochran-Mantel-Haenszel test, stratified by gender and analysis site. P-values marked with * are statistically significant under Hochberg's method.

Subjects who cleared were to enter a 12-week follow-up period for recurrence. Approximately 67% of the subjects who achieved complete clearance were both followed for recurrence for at least 12 weeks and remained clear during the follow-up period.

The local skin reactions of erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration were actively assessed during the study period. All of these events increased during active treatment with imiquimod, and returned to baseline levels after treatment.

1.2 Brief Overview of Clinical Studies

The development program for Zyclara for genital warts consisted of two studies of identical design that compared two doses of imiquimod cream (3.75% and 2.5%) to vehicle using a treatment regimen of once daily use for up to 8 weeks. Both studies were conducted in the United States. The primary efficacy endpoint was complete clearance of all lesions by Week 16. The applicant is seeking approval for Zyclara (imiquimod) cream 3.75% in the treatment of genital warts. Zyclara is currently on the market with an indication of the treatment of actinic keratoses. The clinical study program for Zyclara for genital warts is presented in Table 2.

Table 2 – Clinical Study Program for Zyclara for Genital Warts

Study	Regimen	Treatment Arms	No. of Subjects
GW01-0801	Daily for up to 8 weeks	3.75% imiquimod cream	195
		2.5% imiquimod cream	178
		Vehicle	97
GW01-0805	Daily for up to 8 weeks	3.75% imiquimod cream	204
		2.5% imiquimod cream	202
		Vehicle	105

1.3 Statistical Issues and Findings

The applicant has demonstrated that imiquimod cream 3.75% applied once daily for up to 8 weeks is superior to vehicle in the treatment of genital warts in two studies. The other concentration of imiquimod evaluated in the clinical studies (2.5%) was superior to vehicle in only one of the two studies, and therefore efficacy has not been established for the 2.5% concentration in the treatment of genital warts.

Both studies had relatively high dropout rates of around 30%, with most of the dropout due to loss to follow-up. Because complete clearance could be achieved at any visit up to Week 16 and any subject who achieved complete clearance was considered to have completed the study, subjects who dropped out before achieving complete clearance were all classified as non-responders.

Complete clearance rates were higher for females than males (see Table 3). Also, clearance rates varied across different anatomical regions within the genital area. In particular, the clearance rate for lesions on the penis shaft was lower than for other regions, and a high proportion of males (84%) had lesions on the penis shaft.

Table 3 - Complete Clearance Rates by Gender

Study	Gender	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
0801	Male	19/95 (20%)	11/83 (13%)	2/47 (4%)
	Female	34/100 (34%)	23/95 (24%)	8/50 (16%)
0805	Male	15/88 (17%)	13/85 (15%)	2/49 (4%)
	Female	45/116 (39%)	37/117 (32%)	7/56 (13%)

Local skin reactions were assessed at each visit. Most subjects treated with imiquimod 3.75% experienced local skin reactions, particularly erythema (76%) and edema (44%). The highest mean severity score for local skin reactions was observed at Weeks 2 and 4. Approximately one-third of imiquimod 3.75% subjects required rest periods from treatment.

2 Introduction

2.1 Overview

The applicant markets two imiquimod products: Aldara (5%) and Zyclara (3.75%). Aldara was first approved in 1997 (NDA 20723) and is indicated for actinic keratoses, superficial basal cell carcinoma, and external genital and perianal warts. Zyclara was approved for the indication of actinic keratoses in March 2010 under NDA 22483. This application is for Zyclara for the treatment of external genital and perianal warts. Because the applicant was ready to submit an application for Zyclara for genital warts before the application for Zyclara for actinic keratoses was approved, this application was submitted as an original NDA with a different NDA number (201153).

The approved external genital warts (EGW) indication for Aldara is the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older. The labeled dosing regimen for Aldara is to apply treatment 3 times per week to external genital/perianal warts until total clearance of the warts or for a maximum of 16 weeks. Aldara Cream is to be applied prior to normal sleeping hours and left on the skin for 6 -10 hours, after which time the cream should be removed by washing the area with mild soap and water.

With Zyclara, the applicant has requested labeling for the indication the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older. The applicant has requested a dosing regimen of application once-a-day to the external genital/perianal warts for up to 8 weeks. The proposed treatment regimen for Zyclara differs from Aldara in that it is a lower dose concentration (3.75% vs. 5%), used more frequently (daily vs. 3 times per week), and used for a shorter time period (up to 8 weeks vs. up to 16 weeks).

The applicant conducted two identical Phase 3 studies, Studies 0801 and 0805. Each study evaluated 3.75% imiquimod, 2.5% imiquimod, and vehicle with daily treatment for up to 8 weeks. These two studies will be the focus of the review. Although the Agency requested that the applicant conduct a study which compared the 3.75% imiquimod regimen to the 5% imiquimod regimen to gain an understanding of the relative benefit and risk of the two regimens (see the minutes of the meetings held 7/27/2007, 1/20/2008, and 5/20/2008 and the advice letter dated 8/29/2008 under IND 30,432), the applicant elected not to conduct any comparative studies with the 5% cream.

2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was in hybrid CTD electronic/paper format. The datasets used in this review are archived at \\Fdswa150\nonectd\N201153\N_000\2010-02-05\m5\datasets.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study Design

Studies GW01-0801 and GW01-0805 were randomized, double-blind studies of 2.5% imiquimod, 3.75% imiquimod and vehicle cream in the treatment of external genital warts (EGW). At baseline, subjects were to be at least 12 years of age and have 2-30 genital/perianal warts with a total wart area of at least 10 mm^2 located in the inguinal, perineal, or perianal areas (both sexes); on the glans penis, penis shaft, scrotum, or foreskin (men); or on the vulva (women). Subjects applied study drug in a thin layer to the warts once daily until all warts were cleared or for a maximum of 8 weeks. Study drug was applied prior to normal sleeping hours and removed with soap and water approximately 8 hours later. Subjects were stratified by gender and randomized in a 2:2:1 ratio to 3.75% imiquimod, 2.5% imiquimod, and vehicle.

The primary efficacy endpoint was complete clearance of all warts (baseline and new) on or before Week 16 (end of study), as determined by the investigator. The secondary efficacy endpoints were

- at least 75% reduction in the number of baseline warts on or before Week 16
- percent change from baseline to end of study in total number of warts
- sustained clearance of warts through the end of the follow-up period for recurrence
- time to complete clearance of all warts

According to the statistical analysis plan, the complete and partial clearance efficacy endpoints were analyzed with a Cochran-Mantel-Haenszel (CMH) test stratified on analysis center and gender. Note that the protocol itself stated only that the CMH test would be stratified on analysis center. Percent change from baseline in wart count was analyzed using analysis of covariance, controlling for baseline wart count, gender, and analysis center. Time to complete clearance was analyzed using the log rank test (Kaplan-Meier survival analysis). The proportion of subjects who cleared and remained clear through the follow-up period were summarized with frequency counts and 95% confidence intervals.

Hochberg's procedure was used to control for multiplicity due to multiple doses. That is, if the least significant (larger p-value) dose is significant at 0.05 then both doses are declared significant, otherwise if the larger p-value is larger than 0.05 but the smaller p-value is less than 0.025, then the dose associated with the smaller p-value is declared significant. The secondary endpoints were to be tested in the order listed.

The primary method of handling missing data was last observation carried forward (LOCF), with taking missing values as failures used as a sensitivity analysis. The ITT population was defined as all randomized subjects. The per protocol population excluded subjects who failed to meet the inclusion/exclusion criteria, took restricted medications, did not adhere to the visit schedule, or were non-compliant with study treatment.

3.1.2 Subject Disposition

Approximately 70% of subjects completed the evaluation period in each study, which was defined as either the first visit where complete clearance was observed or Week 16, whichever came first. The most common reasons for discontinuation were lost to follow-up (approximately 20% of subjects) and subject request (approximately 5% of subjects). Discontinuation rates in each category were similar across treatment arms in both studies. See Table 4 and Table 5.

Table 4 – Disposition of Subjects (Study 0801)

	3.75% Imiq.	2.5% Imiq.	Vehicle
Subjects Randomized	195	178	97
Completed evaluation period	136 (70%)	121 (68%)	66 (68%)
Discontinued evaluation period	59 (30%)	57 (32%)	31 (32%)
Reasons for discontinuation			
Safety reasons (AEs)	3 (2%)	2 (1%)	1 (1%)
Investigator request	1 (<1%)	--	--
Subject's request (not AE)	10 (5%)	8 (5%)	7 (7%)
Lack of efficacy	--	1 (<1%)	--
Noncompliance	1 (<1%)	4 (2%)	--
Concomitant therapy	--	--	--
Lost to follow-up	39 (20%)	37 (21%)	19 (20%)
Other (not AE)	5 (3%)	5 (3%)	4 (4%)

Source: pg 59 of study report (\\Fdswa150\nonectd\N201153\N_000\2010-02-05\m5\53-clin-stud-rep\535-rep-effic-safety-stud\egw\5351-stud-rep-contr\gw01-0801\gw01-0801a.pdf)

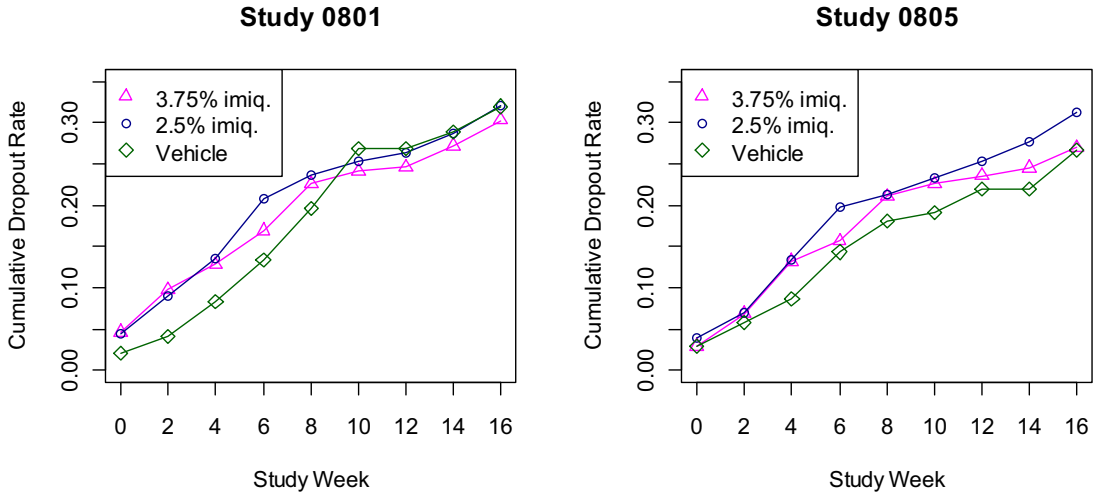
Table 5 – Disposition of Subjects (Study 0805)

	3.75% Imiq.	2.5% Imiq.	Vehicle
Subjects Randomized	204	202	105
Completed evaluation period	149 (73%)	139 (69%)	77 (73%)
Discontinued evaluation period	55 (27%)	63 (31%)	28 (27%)
Reasons for discontinuation			
Safety reasons (AEs)	3 (2%)	4 (2%)	--
Investigator request	2 (1%)	--	1 (1%)
Subject's request (not AE)	11 (5%)	10 (5%)	4 (4%)
Lack of efficacy	--	--	--
Noncompliance	2 (1%)	3 (2%)	3 (3%)
Concomitant therapy	--	1 (<1%)	--
Lost to follow-up	35 (17%)	40 (20%)	19 (18%)
Other (not AE)	2 (1%)	5 (2%)	1 (1%)

Source: pg 58 of study report (\\Fdswa150\nonectd\N201153\N_000\2010-02-05\m5\53-clin-stud-rep\535-rep-effic-safety-stud\egw\5351-stud-rep-contr\gw01-0805\gw01-0805a.pdf)

Due to the relatively high proportion of dropouts, it may be of interest to know whether subjects were more likely to drop out early or late in the trial. Figure 1 presents the cumulative dropout rate by study week. More of the dropout occurred during the first 8 weeks of the study (the treatment period) rather than the post-treatment period; however there are no substantial differences in the rates for the different treatment arms. Note however, that subjects who cleared at any visit exited the first stage of the study and entered the follow-up period, so that those subjects remaining until the later visits all were non-responders.

Figure 1 – Dropout Rate by Week



3.1.3 Baseline Characteristics

Baseline demographics for age, gender, race, and ethnicity were generally balanced across treatment groups in Studies 0801 and 0805. Slightly more than half of the subjects were female and the average age was around 33 years. Only two subjects less than 18 years of age were treated with 3.75% imiquimod (age 15 and 16) and one 17 year-old subject was treated with 2.5% imiquimod in the two studies. The baseline demographics are presented in Table 6 and Table 7.

Table 6 – Baseline Demographics (Study 0801)

	3.75% Imiq. N=195	2.5% Imiq. N=178	Vehicle N=97
Age (years)			
Mean	32.5	32.7	30.5
Range	18 - 81	17 - 78	18 - 75
≤ 17 years	--	1 (<1%)	--
18 – 64 years	192 (98%)	176 (99%)	95 (98%)
≥ 65 years	3 (2%)	1 (<1%)	2 (2%)
Gender			
Male	95 (49%)	83 (47%)	47 (49%)
Female	100 (51%)	95 (53%)	50 (51%)
Ethnicity			
Hispanic	31 (16%)	25 (14%)	11 (11%)
Non-Hispanic	164 (84%)	153 (86%)	86 (89%)
Race			
White	147 (75%)	122 (69%)	66 (68%)
Black	41 (21%)	47 (26%)	28 (29%)
Other	7 (4%)	9 (5%)	3 (3%)

Source: pg 65 of study report (\\Fdswa150\nonectd\N201153\N_000\2010-02-05\m5\53-clin-stud-rep\535-rep-effic-safety-stud\egw\5351-stud-rep-contr\gw01-0801\gw01-0801a.pdf)

Table 7 – Baseline Demographics (Study 0805)

	3.75% Imiq. N=204	2.5% Imiq. N=202	Vehicle N=105
Age (years)			
Mean	32.8	33.1	33.3
Range	15 - 70	18 - 60	19 - 66
≤ 17 years	2 (1%)	--	--
18 – 64 years	200 (98%)	202 (100%)	104 (99%)
≥ 65 years	2 (1%)	--	1 (1%)
Gender			
Male	88 (43%)	85 (42%)	49 (47%)
Female	116 (57%)	117 (58%)	56 (53%)
Ethnicity			
Hispanic	12 (6%)	21 (10%)	8 (8%)
Non-Hispanic	192 (94%)	181 (90%)	97 (92%)
Race			
White	141 (69%)	133 (66%)	76 (72%)
Black	55 (27%)	66 (33%)	27 (26%)
Other	8 (4%)	3 (2%)	2 (2%)

Source: pg 66 of study report (\\Fdswa150\nonectd\N201153\N_000\2010-02-05\m5\53-clin-stud-rep\535-rep-effic-safety-stud\egw\5351-stud-rep-contr\gw01-0805\gw01-0805a.pdf)

The median number of warts at baseline was about 7 warts. The median total wart area at baseline was around 60 mm^2. The distributions of the number of warts and total wart area at baseline were quite skewed. In particular a small number of subjects (<5%) had

very large wart areas at baseline (>1000 mm^2) relative to the median wart area of around 60 mm^2. The skewed distribution leads to very different estimates for the mean and median wart area (mean of approximately 160 versus a median of approximately 60). See Table 8 and Table 9. Note that some of the very large wart areas were on subjects with only two baseline warts. For example, of the 110 subjects with two warts at baseline (in the two studies combined), 5 (5%) had a total wart area > 1000 mm^2; that is an average area per wart of >500 mm^2, comparable to warts of size 22 mm by 22 mm.

Table 8 – Baseline Wart Characteristics (Study 0801)

	3.75% Imiq. N=195	2.5% Imiq. N=178	Vehicle N=97
Total Wart Area (mm^2)			
Mean (SD)	150.9 (458.7)	160.2 (334.8)	140.7 (248.6)
Minimum	10	10	6
Q1	25	22	27
Median	52	68	73
Q3	120	140	137
Maximum	5579	3212	1969
Total Wart Count			
Mean (SD)	8.6 (6.4)	9.2 (6.7)	11.6 (8.8)
Minimum	2	2	2
Q1	4	4	5
Median	7	7	8
Q3	12	12	17
Maximum	30	30	30

Source: pg 67 of study report (\\Fdswa150\nonectd\N201153\N_000\2010-02-05\m5\53-clin-stud-rep\535-rep-effic-safety-stud\egw\5351-stud-rep-contr\gw01-0801\gw01-0801a.pdf) and reviewer analysis.

Table 9 – Baseline Wart Characteristics (Study 0805)

	3.75% Imiq. N=204	2.5% Imiq. N=202	Vehicle N=105
Total Wart Area (mm^2)			
Mean (SD)	150.2 (321.9)	161.1 (367.4)	200.7 (374.9)
Minimum	9	10	10
Q1	26	22	24
Median	61	53	61
Q3	124.5	126	141
Maximum	3419	4000	1950
Total Wart Count			
Mean (SD)	8.7 (7.5)	7.7 (6.2)	7.7 (6.3)
Minimum	2	2	2
Q1	3	3	3
Median	6	5	6
Q3	11.5	10	10
Maximum	48	30	29

Source: pg 69 of study report (\\Fdswa150\nonectd\N201153\N_000\2010-02-05\m5\53-clin-stud-rep\535-rep-effic-safety-stud\egw\5351-stud-rep-contr\gw01-0805\gw01-0805a.pdf) and reviewer analysis.

3.1.4 Primary Efficacy Results

The primary efficacy endpoint was complete clearance of all warts (baseline and new) on or before Week 16 (end of study). Approximately 28% of imiquimod 3.75% subjects achieved complete clearance by Week 16 versus 9% of vehicle subjects. The p-values were computed using a CMH test stratifying on analysis center and gender. Hochberg's method was used to control for multiplicity due to two dose levels. In Study 0801 the p-value for imiquimod 2.5% versus vehicle was > 0.05, but the p-value for imiquimod 3.75% versus vehicle was <0.025. In Study 0805, the p-values for both doses were <0.05. Therefore, imiquimod 3.75% was superior to vehicle in both studies, but imiquimod 2.5% was superior to vehicle only in Study 0805. See Table 10. Results in the per protocol population are similar, and a few percentage points higher across all treatment arms (see Table 11).

Table 10 - Complete Clearance Rates at End of Study (ITT)

Study	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
0801	53/195 (27%) 0.001*	34/178 (19%) 0.065	10/97 (10%)
0805	60/204 (29%) <0.001*	50/202 (25%) 0.001*	9/105 (9%)

P-values (vs. vehicle) are from Cochran-Mantel-Haenszel test, stratified by gender and analysis site. P-values marked with * are statistically significant under Hochberg's method.

Table 11 - Complete Clearance Rates at End of Study (PP)

Study	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
0801	46/137 (34%) <0.001*	32/134 (24%) 0.044*	9/76 (12%)
0805	49/144 (34%) <0.001*	43/144 (30%) 0.001*	9/81 (11%)

P-values (vs. vehicle) are from Cochran-Mantel-Haenszel test, stratified by gender and analysis site. P-values marked with * are statistically significant under Hochberg's method.

The protocol and statistical analysis plan listed slightly different stratifying factors for the primary analysis. The protocol stated that the CMH test would be stratified based on the analysis site, while the statistical analysis plan stated that the analysis would be stratified based on analysis site and gender. Otherwise the analyses described in the statistical analysis plan are consistent with the protocol. Note that gender and site were both stratification factors under the randomization. Because the earliest specification of the analysis (in the protocol) was to stratify only on the analysis site, the p-values from this analysis are presented in Table 12 for comparison. The p-values are very similar in the two analyses, and the conclusions of the studies remain the same under either analysis.

Table 12 – P-values using only Analysis Site as Stratification Factor (ITT)

Study	Imiq. 3.75% vs. Vehicle	Imiq. 2.5% vs. Vehicle
0801	0.001*	0.058
0805	<0.001*	0.001*

P-values (vs. vehicle) are from Cochran-Mantel-Haenszel test, stratified by analysis site. P-values marked with * are statistically significant under Hochberg's method.

3.1.5 Secondary Efficacy Endpoints

The secondary efficacy endpoints were

- at least 75% reduction in the number of baseline warts (partial clearance) on or before Week 16
- percent change from baseline to end of study in total number of warts
- sustained clearance of warts through the end of the follow-up period for recurrence
- time to complete clearance of all warts

Approximately 10% of imiquimod 3.75% subjects achieved partial clearance but not complete clearance (38% achieved partial clearance including 28% who achieved complete clearance). Correspondingly, approximately 1.5% of vehicle subjects achieved partial clearance by not complete clearance (11.9% vs. 9.4%). Note, however, that many subjects had only 2 or 3 lesions at baseline (approximately 25% of imiquimod 3.75% subjects), and therefore could achieve ≥ 75% clearance only be achieving complete clearance. Also, because of the variability in the size of lesions at baseline (some subjects had very large baseline wart areas), but the corresponding area measurements are not available at any post-baseline visits, it may be harder to interpret the results of partial clearance. However, the results of the partial clearance rate analysis are consistent with the complete clearance rate analysis (see Table 13). According to the table with the change and percent change from baseline results (Table 14), imiquimod 3.75% had a mean reduction of about 4 lesions (median of 2 lesions) compared to a mean reduction of about 1 lesion (median of 0 lesions) for vehicle subjects. In terms of percent reduction, imiquimod 3.75% subjects had reductions of 40-50% using both the mean and median, compared to a mean percent reduction of about 8% (median of 0%) for vehicle subjects.

Table 13 – Partial (≥75%) Clearance Rates at End of Study (ITT)

Study	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
0801	74/195 (38%)	48/178 (27%)	13/97 (13%)
0805	79/204 (39%)	63/202 (31%)	11/105 (10%)

Table 14 – Change and Percent Change from Baseline in Lesion Count (ITT)

0801	3.75% Imiq. N=195		2.5% Imiq. N=178		Vehicle N=97	
	Mean	*Med*	*Mean*	*Med*	*Mean*	*Med*
Baseline	8.6	7	9.2	7	11.6	7
Change	-4.1	-2	-2.4	-1	-1.5	0
% Change	-45.8	-50	-26.6	-14.6	-9.4	0
0805	3.75% Imiq. N=204		2.5% Imiq. N=202		Vehicle N=105	
	Mean	*Med*	*Mean*	*Med*	*Mean*	*Med*
Baseline	8.7	6	7.7	5	7.7	6
Change	-3.7	-2	-3	-1	-0.6	0
% Change	-40.9	-46.8	-37.7	-19.1	-7.8	0

Sustained clearance and recurrence of lesions are discussed in Section 3.1.11. Time to complete clearance is discussed in Section 3.1.8.

3.1.6 Efficacy Results by Gender

Gender was a factor of special interest; the randomization was stratified on gender. Additionally previous studies in imiquimod in genital warts (using Aldara 5%) had demonstrated different response rates in males and females. However, the protocol only specified a by gender analyses as part of a standard battery of subgroup analyses (gender, age, baseline count and area, anatomical location.) As noted previously, the protocol and statistical analysis plan did not agree as to whether gender was a factor to be accounted for in the primary analysis. Complete clearance rates were higher in females than in males across all treatment arms. However, the treatment effects for imiquimod 3.75% versus vehicle were fairly similar in Study 0801 (18% for females and 16% for males), but were more different in Study 0805 (26% for females and 13% for males). See Table 15. See also the following section regarding efficacy by lesion location.

Table 15 - Complete Clearance Rates by Gender

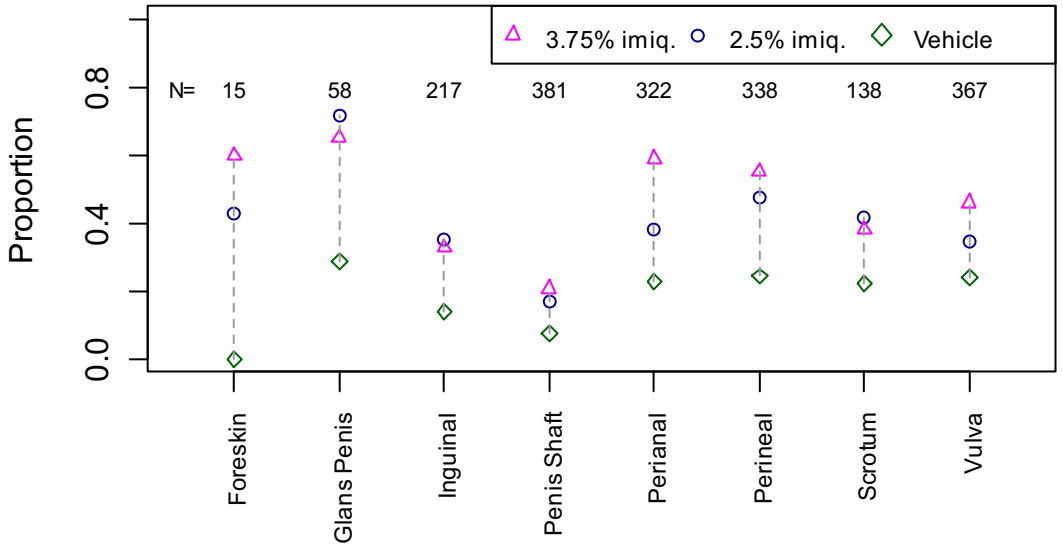
Study	Gender	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
0801	Male	19/95 (20%)	11/83 (13%)	2/47 (4%)
	Female	34/100 (34%)	23/95 (24%)	8/50 (16%)
0805	Male	15/88 (17%)	13/85 (15%)	2/49 (4%)
	Female	45/116 (39%)	37/117 (32%)	7/56 (13%)

3.1.7 Efficacy by Lesion Location

Male subjects could have lesions on any of up to 7 anatomical regions (foreskin, glans penis, penis shaft, scrotum, inguinal, perianal, and perineal) and female subjects could have lesions on up to 4 anatomical regions (vulva, inguinal, perianal, and perineal). The most common region for males was the penis shaft with 84% of male subjects having lesions in this region at baseline. The next most common regions for males were the scrotum and inguinal areas with approximately 22-28% of male subjects having lesions in these regions. About half of the male subjects had lesions in two or more regions.

For females, the most common region was the vulva with 62-68% of subjects having vulvar lesions. The next most common regions for females were the perineal and perianal regions with 45-49% of subjects. Approximately 55% of female subjects had lesions in two or more regions. Among the regions with the larger sample sizes (> 100 subjects across the three treatment arms), the highest response rates for imiquimod 3.75% were the perianal and perineal regions. The region with the smallest response rates was the penis shaft. The lower response rate in males appears to be driven by the lower response rate in the penis shaft (84% of males had lesions in this region). See Figure 2.

Figure 2 – Complete Clearance Rates within Regions (Combined Studies)

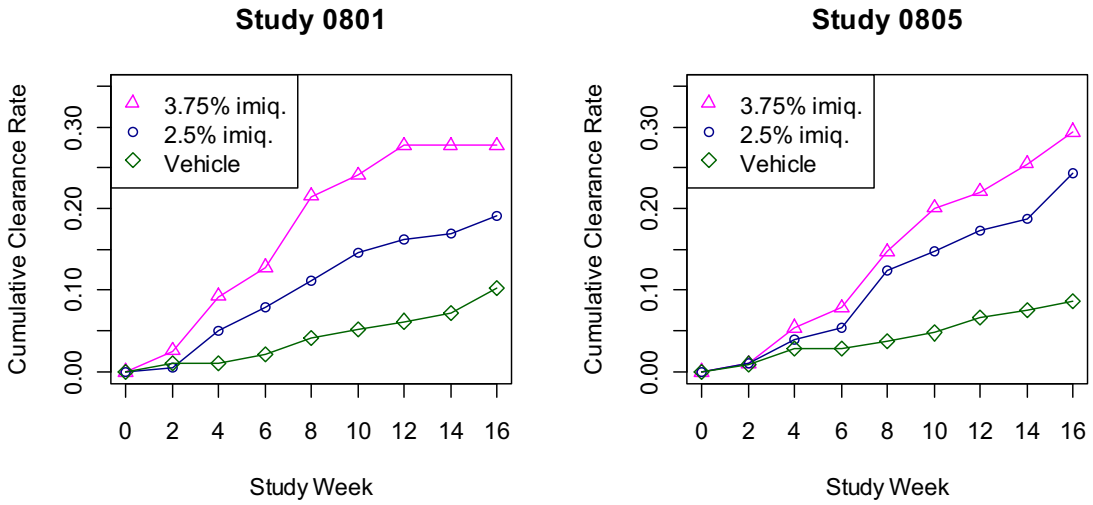


Note: N represents the number of subjects with lesions in the given region. Subjects could have lesions in more than one region.

3.1.8 Efficacy over Time

Subjects were classified as reaching the 'end of study' at the first visit where complete clearance was observed (or Week 16 if complete clearance had not been achieved). After complete clearance was achieved, subjects entered a follow-up period for recurrence. The cumulative number of complete responders by Week 16 is presented in Figure 3. Although the final complete clearance rates were similar for the two studies, imiquimod 3.75% subjects in Study 0801 reached complete clearance earlier than those is Study 0805. By the end of the scheduled treatment period (8 weeks) 22% of imiquimod 3.75% subjects in Study 0801 and 15% of imiquimod 3.75% subjects in Study 0805 had achieved complete clearance. By the end of the study (16 weeks) 27% and 29% of imiquimod 3.75% subjects in the two studies respectively had achieved complete clearance.

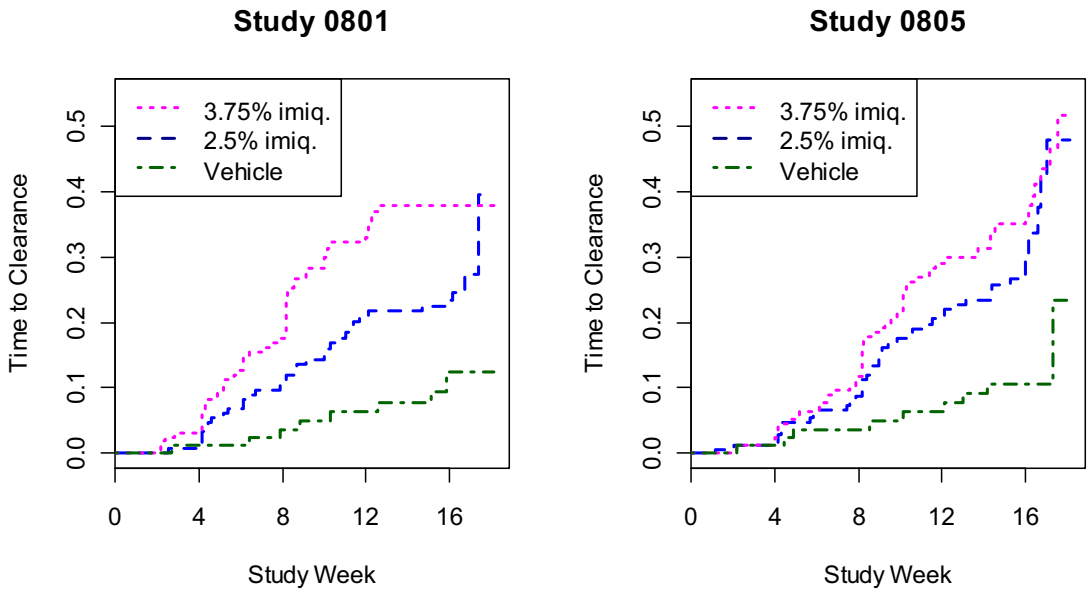
Figure 3 – Cumulative Complete Clearance Rates by Study Week



3.1.9 Impact of Dropouts and Time to Event

Approximately 30% of subjects dropped out of the study. Subjects who achieved complete clearance at any visit by Week 16 were classified as having an end-of-study status of 'cleared'. Therefore all subjects who discontinued prior to Week 16 were by definition 'not cleared' and classified as failures. An alternate way of handling the missing data would be to conduct a time to event analysis using Kaplan-Meier methods. This analysis would be expected to lead to higher estimates for the complete clearance rate, as the Kaplan-Meier estimates assume that the subjects who drop out respond similarly to those who remain in the study (some successes, some failures), rather than treating them all as failures. This can be seen in Figure 4, where the estimated proportion of responders by the end of the study for imiquimod 3.75% was about 38% in Study 0801 and 52% in Study 0805. Note also that Kaplan-Meier estimates can be very sensitive to 'late-occurring' events when most subjects are censored at a fixed timepoint (16 weeks in this case). Thus a subject who comes in as a responder at the last visit and also comes in 'late' for the visit (say at 17 weeks when most subjects have reported for the last visit by 16 ½ weeks) will have a larger influence on the final estimate as very few subjects may still be 'at risk' (not responded and not yet attended the final visit.) An example of this is seen in Study 0801 (Figure 4) for the 2.5% imiquimod arm which 'spikes' after Week 16 due to a late-reporting subject. Therefore the maximum clearance rates from the Kaplan-Meier analysis should be interpreted with caution. Since fewer than half of the subjects responded by Week 16, it is not possible to estimate the median time to clearance.

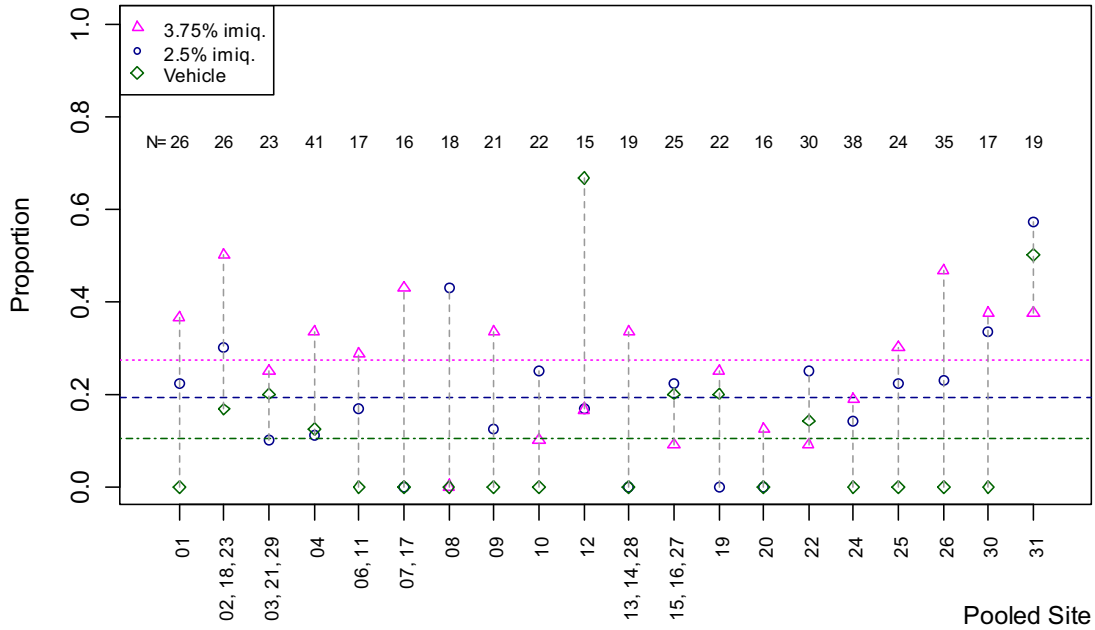
Figure 4 – Kaplan-Meier Estimates for Time to Clearance



3.1.10 Efficacy by Center

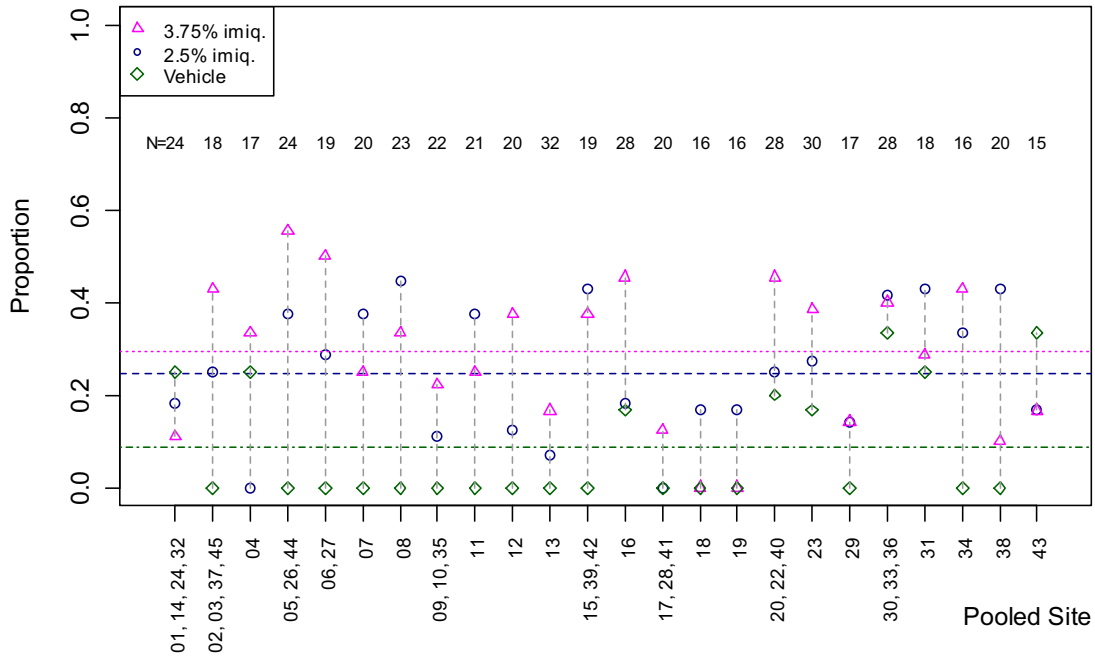
The complete clearance rates within each center for the two studies are fairly similar with no individual centers dominating the results. Some centers were small and pooled with other centers for the analyses that take center into account. See Figure 5 and Figure 6.

Figure 5 – Complete Clearance Rate by Pooled Site (Study 0801)



Note: N represents the total sample size for the pooled site.

Figure 6 – Complete Clearance Rate by Pooled Site (Study 0805)



Note: N represents the total sample size for the pooled site.

3.1.11 Recurrence Rates

Subjects who were cleared of all lesions at any visit at or before Week 16 (end of study visit) were to be entered into a 12-week follow-up period to assess for recurrence.

Table 16 – Recurrence Classification for Subjects Responding at End of Study (Study 0801)

	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Responders	53	34	10
No follow-up for recurrence	4	3	4
Subjects with < 12 weeks (≤ 71 days) follow-up but no recurrence	2	6	0
- 4 weeks	-	*4*	-
- 8 weeks	*2*	*2*	-
No recurrence with 12 weeks follow-up (visit within Day 72 – 99 window)	37	15	5
No recurrence with > 99 days follow-up	3	4	1
Recurrence within 12 weeks (99 days)	7	6	0
-By Week 4	*3*	*4*	-
-By Week 8	-	*2*	-
-By Week 12	*4*	-	-

Table 17 – Recurrence Classification for Subjects Responding at End of Study (Study 0805)

	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Responders	60	50	9
No follow-up for recurrence	7[a]	7	2
Subjects with < 12 weeks (≤ 71 days) follow-up but no recurrence	7[a]	4	0
- 4 weeks	*4*	*2*	-
- 8 weeks	*3*	*2*	-
No recurrence with 12 weeks follow-up (visit within Day 72 – 99 window)	34	29	7
No recurrence with > 99 days follow-up	2	3	0
Recurrence within 12 weeks (99 days)	10	7	0
-By Week 4	*5*	*3*	-
-By Week 8	*2*	*1*	-
-By Week 12	*3*	*3*	-

[a]Subject 10/013 was followed for 42 days after achieving clearance at Day 58. However, this subject was not considered to have entered the Follow-up Period (the Day 100 visit was classified as the End of Study visit). This subject is included under the 'no follow-up' category, though this subject could be considered to have had 4 weeks of follow-up post clearance.

When classifying subjects as having a recurrence, not having a recurrence, or having incomplete follow-up, the applicant and the reviewer used slightly different criteria which led to different numerators and denominators. These differences are summarized in Table 18. In particular, the applicant excluded subjects without any follow-up from the denominator. In addition, to be classified as not having a recurrence by the applicant, a subject must have had a visit between Days 72 and 99; subjects who may have been followed longer than 99 days without recurrence were counted as missing.

Table 18 – Differences between Applicant and Rate Definitions

	Applicant	Reviewer
Denominator	End of Study responders with at least 1 visit in the follow-up period	End of Study responders
Numerator for recurrence	Recurrence within 99 days follow-up	Recurrence within 99 days follow-up
Numerator for non-recurrence	No recurrence and visit within Day 72-99 of follow-up period	No recurrence and a visit on Day 72 or later of follow-up period
Numerator for missing	No recurrence and no visit within Day 72-99 of follow-up period	No recurrence and no visit on Day 72 or later of follow-up period

For the imiquimod 3.75% results, the differences between the applicant's and the reviewer's analyses are small (1- 4%). However, due the small number of vehicle subjects who cleared and entered the recurrence period, the handling of missing data has

a greater impact on the non-recurrence rate estimate on the vehicle arm. In the two studies, 60-75% of imiquimod 3.75% subjects who had complete clearance and remained in the study for at least 12 weeks of follow-up remained clear of lesions, while 13-17% had observed recurrence and 11-23% had less than 12 weeks of follow-up and their final status is missing. The applicant and reviewer analyses are presented in Table 19 and Table 20. None of the vehicle subjects had recurrence, however, 22-40% of the vehicle subjects did not have complete follow-up.

Table 19 – Differences between Applicant and Reviewer Non-recurrence Rates (Study 0801)

	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Applicant rates			
Recurrence	7/49 (14%)	6/31 (19%)	0/6 (0%)
Non-recurrence	37/49 (76%)	15/31 (48%)	5/6 (83%)
Missing	5/49 (10%)	10/31 (32%)	1/6 (17%)
Reviewer rates			
Recurrence	7/53 (13%)	6/34 (18%)	0/10 (0%)
Non-recurrence	40/53 (75%)	19/34 (56%)	6/10 (60%)
Missing	6/53 (11%)	9/34 (26%)	4/10 (40%)

Table 20 – Differences between Applicant and Reviewer Non-recurrence Rates (Study 0805)

	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Applicant rates			
Recurrence	10/53 (19%)	7/43 (16%)	0/7 (0%)
Non-recurrence	34/53 (64%)	29/43 (67%)	7/7 (100%)
Missing	9/53 (17%)	7/43 (16%)	0/7 (0%)
Reviewer rates			
Recurrence	10/60 (17%)	7/50 (14%)	0/9 (0%)
Non-recurrence	36/60 (60%)	32/50 (64%)	7/9 (78%)
Missing	14/60 (23%)	11/50 (22%)	2/9 (22%)

3.2 Evaluation of Safety

3.2.1 Extent of Exposure

Extent of exposure is difficult to evaluate in these trials because subjects were to stop treatment when clearance was achieved. Thus short treatment durations could imply either complete clearance before Week 8 or early dropout. Subjects were permitted to take rest periods during treatment due to local skin reactions and this could reduce the number of days treated. The studies also had relatively high dropout rates, so a number of subjects do not have their extent of exposure recorded. Table 21 and Table 22 present the number of days treated by study completion status. As expected, subjects who did not respond, but remained in the study the whole time had the largest number of days treated, ranging from about 50-51 days for imiquimod subjects and 54-55 days for

vehicle subjects. Responding subjects using imiquimod treated for an average of 38-41 days, while the responding subjects using vehicle treated for an average for 45-47 days. As most of the subjects without information on duration were also dropouts, it is difficult to estimate how many days subjects who dropped out used treatment.

Table 21 – Mean Number of Days Treated by Study Completion Status (Study 0801)

	Imiquimod 3.75% N=195	Imiquimod 2.5% N=178	Vehicle N=97
Responders	N=52 38.5	N=34 38.0	N=10 47.2
Non-Responders[a]	N=80 50.2	N=84 50.0	N=56 54.2
Dropouts	N=35 33.6	N=27 34.7	N=21 41.4
All subjects with data	N=167 43.1	N=145 44.3	N=87 50.3
No duration data	N=28	N=33	N=10

[a]Completed treatment period but did not achieve complete clearance

Table 22 – Mean Number of Days Treated by Study Completion Status (Study 0805)

	Imiquimod 3.75% N=204	Imiquimod 2.5% N=202	Vehicle N=105
Responders	N=59 39.4	N=46 41.6	N=9 45.4
Non-Responders[a]	N=86 51.3	N=89 51.9	N=67 55.2
Dropouts	N=27 28.6	N=28 32.2	N=13 40.0
All subjects with data	N=172 43.7	N=163 45.6	N=89 51.9
No duration data	N=32	N=39	N=16

[a]Completed treatment period but did not achieve complete clearance

Approximately 32% of imiquimod 3.75% subjects required rest periods, compared to 28% of imiquimod 2.5% subjects and 2% of vehicle subjects. The mean number of missed days due to rest periods was around 8-10 days with a maximum of 36 days for imiquimod 3.75% subjects. The mean number of dosing days completed before the first rest period was around 18 days for imiquimod 3.75%. See Table 23.

Table 23 – Rest Periods

	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Subjects Requiring Rest Periods			
Study 0801	59/195 (30%)	49/178 (28%)	1/97 (1%)
Study 0805	67/204 (33%)	55/202 (27%)	3/105 (3%)
Mean (Max) of Dosing Days Missed Due to Rest Period			
Study 0801	7.9 (35)	10.0 (36)	3.0 (3)
Study 0805	10.3 (36)	9.3 (30)	6.7 (12)
Mean (Range) of Dosing Days Prior to First Rest Period			
Study 0801	17.8 (47)	19.3 (45)	15.0 (15)
Study 0805	18.3 (52)	18.9 (58)	25.7 (28)

3.2.2 Local Skin Reactions

At each visit, investigators evaluated six local skin reactions (LSR) on 4-point scales: erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration (erosion/ulceration was measured on a 3-point scale). See the Appendix for the definition of the individual scales. For imiquimod-treated subjects, the mean scores increased during the treatment periods and returned to baseline levels after the treatment period. The highest mean scores for the LSRs occurred at Week 2 or 4. The mean LSR scores were slightly higher in the imiquimod 3.75% arm than in the 2.5% arm. See Figure 7 and Figure 8.

Figure 7 – Mean Local Skin Reaction Scores by Visit (Study 0801)

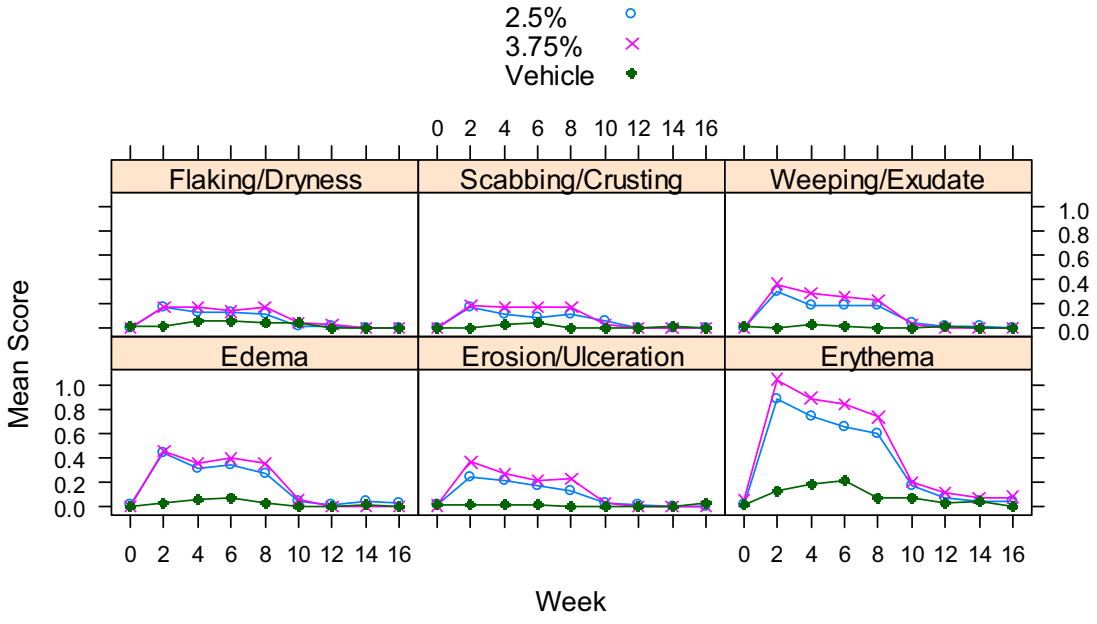


Figure 8 – Mean Local Skin Reaction Scores by Visit (Study 0805)

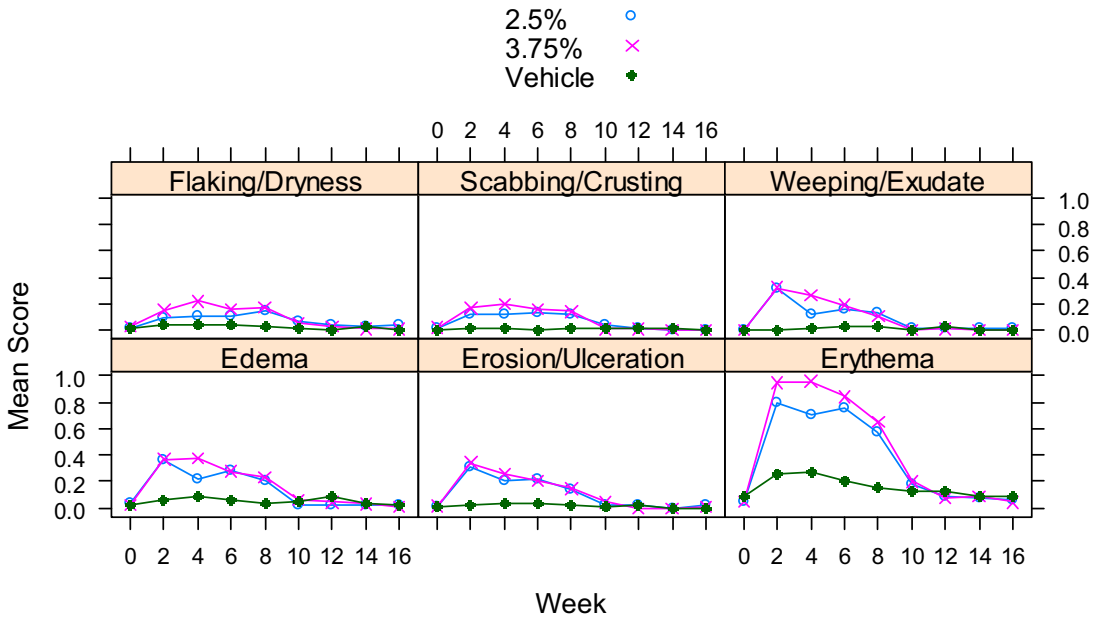


Table 24 tabulates the maximum score observed in subjects during the post-baseline period for each local skin reaction for the studies combined. Due to subject dropout, approximately 7% of subjects did not have any post-baseline assessments. These subjects are excluded from the tabulations. Other subjects who dropped out may not have had assessments during the complete period. If subjects who did not return for assessments dropped out due to intolerable skin reactions, the estimates from the table may be underestimated.

Table 24 – Maximum Local Skin Reaction Severity Post-Baseline in Subjects with at least One Assessment (Combined Studies)

Imiquimod 3.75% (N=369[a])					
	0	1	2	3	≥1
Erythema	89 (24%)	103 (28%)	141 (38%)	36 (10%)	280 (76%)
Edema	206 (56%)	113 (31%)	42 (11%)	8 (2%)	163 (44%)
Erosion/Ulceration	226 (61%)	100 (27%)	43 (12%)	NA	143 (39%)
Weeping/Exudate	234 (63%)	94 (25%)	34 (9%)	7 (2%)	135 (37%)
Flaking/Dryness	251 (68%)	104 (28%)	14 (4%)	0 (0%)	118 (32%)
Scabbing/Crusting	276 (75%)	74 (20%)	16 (4%)	3 (1%)	93 (25%)
Vehicle (N=190[a])					
	0	1	2	3	≥1
Erythema	135 (71%)	39 (21%)	15 (8%)	1 (<1%)	55 (29%)
Edema	174 (92%)	14 (7%)	2 (1%)	0 (0%)	16 (8%)
Erosion/Ulceration	181 (95%)	8 (4%)	1 (<1%)	NA	9 (5%)
Weeping/Exudate	185 (98%)	4 (2%)	1 (<1%)	0 (0%)	5 (2%)
Flaking/Dryness	169 (89%)	20 (11%)	1 (<1%)	0 (0%)	21 (11%)
Scabbing/Crusting	182 (96%)	6 (3%)	2 (1%)	0 (0%)	8 (4%)

[a] Number of subjects with at least one post-baseline assessment

3.2.3 Adverse Reactions

The overall treatment-emergent adverse event rate was similar for the two imiquimod treatment arms (35-36%) but greater than for vehicle (28%) in the combined studies. Treatment-emergent adverse events were defined as those with onset between randomization and 30 days after the end of treatment. Therefore this list does not include all adverse events that occurred in the post-treatment follow-up period. The most common adverse events were application site reactions (pain, irritation, and pruritus) and infections. See Table 25. Note that the adverse reactions specifically assessed as local skin reactions were not recorded as spontaneously reported adverse events unless they extended beyond the treatment area, required medical intervention, or resulted in discontinuation.

Table 25 – Common Adverse Events (≥2%) Reported in Combined Studies

	Imiquimod 3.75% N=400	Imiquimod 2.5% N=379	Vehicle N=202
Any Adverse Event	144 (36%)	134 (35%)	56 (28%)
Most Common Adverse Events			
Application site pain	28 (7%)	20 (5%)	1 (<1%)
Application site irritation	24 (6%)	13 (3%)	2 (1%)
Nasopharyngitis	11 (3%)	14 (4%)	9 (5%)
Application site pruritus	11 (3%)	17 (4%)	2 (1%)
Upper respiratory tract infection	7 (2%)	6 (2%)	3 (2%)
Vaginitis bacterial	6 (2%)	3 (1%)	2 (1%)
Headache	6 (2%)	3 (1%)	1 (<1%)

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4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Females had higher response rates than males, though this was true for all treatment arms (see Figure 9 and Section 3.1.6 for additional discussion). Response rates were more similar across race and age groups, though the older age group (> 35 years) had slightly higher response rates than the younger age group. See Figure 10 and Figure 11.

Figure 9 – Complete Clearance Rates by Gender

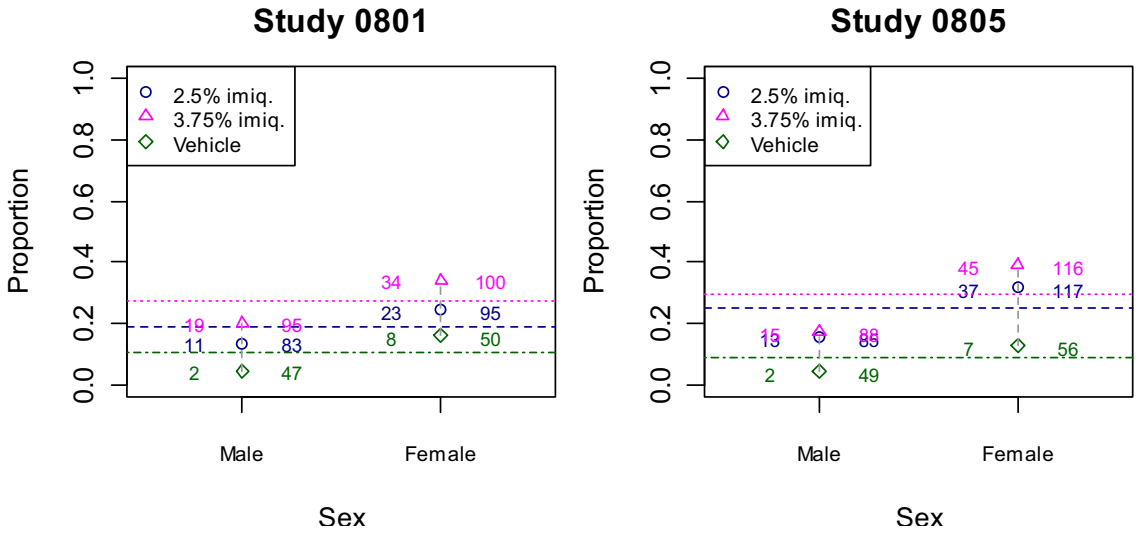


Figure 10 – Complete Clearance Rates by Race

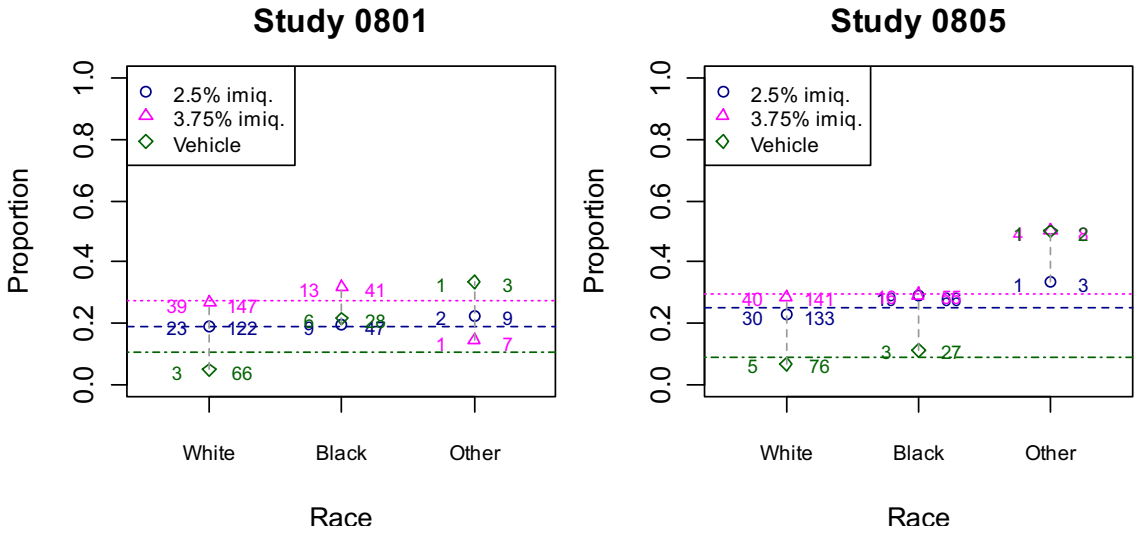
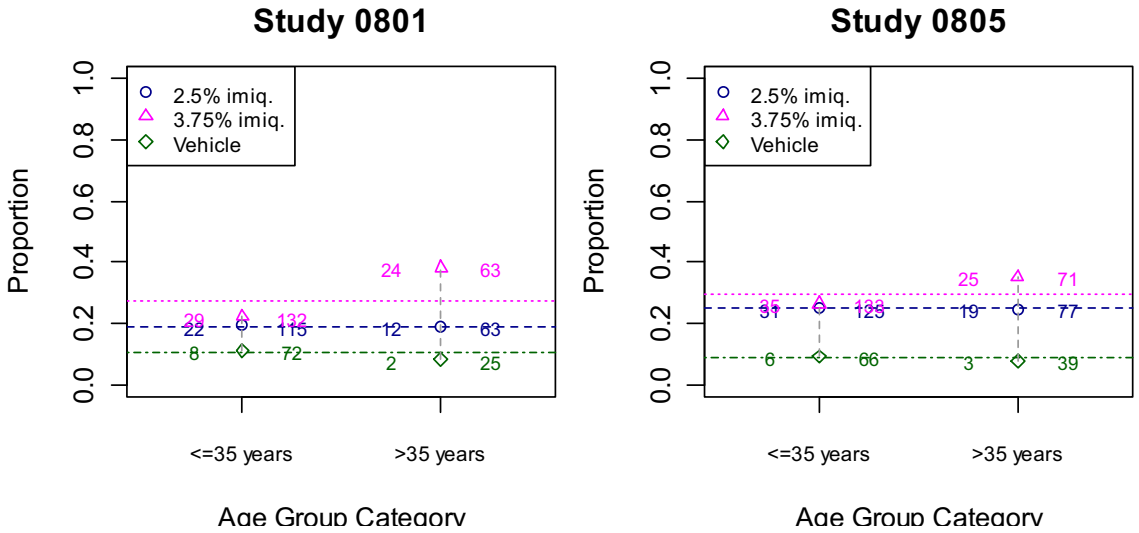


Figure 11 – Complete Clearance Rates by Age Group



4.2 Other Special/Subgroup Populations

Not applicable.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The applicant has demonstrated that imiquimod cream 3.75% applied once daily for up to 8 weeks is superior to vehicle in the treatment of external genital warts in two studies. Both studies had relatively high dropout rates of around 30%, with most of the dropout due to loss to follow-up. Because complete clearance could be achieved at any visit up to Week 16 and any subject who achieved complete clearance was considered to have completed the study, subjects who dropped out before achieving complete clearance were all classified as non-responders.

Complete clearance rates were higher for females than males (37% for females and 19% for males for imiquimod 3.75% vs. 14% for females and 4% for males for vehicle in the combined studies). Clearance rates varied across different anatomical regions. In particular, the clearance rate for lesions on the penis shaft was lower than for other regions, and a high proportion of males (84%) had lesions on the penis shaft.

Local skin reactions were assessed at each visit. Most subjects treated with imiquimod 3.75% experienced local skin reactions, particularly erythema (76%) and edema (44%). The highest mean severity for local skin reactions was observed at Weeks 2 and 4 with severity levels generally returning to baseline levels at the end of the treatment period. Approximately one-third of imiquimod 3.75% subjects required rest periods from treatment with a mean duration of about 9 days.

5.2 Conclusions and Recommendations

Zyclara (imiquimod) cream 3.75% applied once daily for up to 8 weeks was superior to vehicle in the treatment of external genital warts in two studies ($p \leq 0.001$, statistically significant after adjusting for multiplicity due to two dose groups). However, while the efficacy for the 3.75% concentration has been established, as imiquimod cream 2.5% was only superior to vehicle in one of the two studies, efficacy has not been established for the lower concentration of imiquimod. The studies enrolled subjects at least 12 years of age with 2-30 genital/perianal warts with a total wart area of at least 10 mm^2. The primary efficacy endpoint was complete clearance of all warts (baseline and new) on or before Week 16 (end of study), as determined by the investigator. Subjects stopped treatment when complete clearance was achieved. Approximately 28% (113/399) of imiquimod 3.75% subjects achieved complete clearance compared to 9% (19/202) of vehicle subjects in the combined studies.

Subjects who cleared were to enter a 12-week follow-up period for recurrence. Approximately 67% of the subjects who achieved complete clearance were followed for recurrence for at least 12 weeks and remained clear during the follow-up period.

The local skin reactions of erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration were actively assessed during and after treatment. All of these events increased during active treatment with imiquimod, and returned to baseline levels after treatment.

Appendix

Table 26 – Local Skin Reaction Severity Definitions

Local Skin Reaction	Severity Definitions			
	0	1 (Mild)	2 (Moderate)	3 (Severe)
Erythema	None	Faint to mild redness	Moderate redness	Intense redness
Edema	None	Mild visible or barely palpable swelling/induration	Easily palpable swelling/induration	Gross swelling/induration
Weeping/ exudate	None	Minimal exudate	Moderate exudate	Heavy exudate
Flaking/ scaling/ dryness	None	Mild dryness/flaking	Moderate dryness/flaking	Severe dryness/flaking
Scabbing/ crusting	None	Crusting	Serous scab	Eschar

Local Skin Reactions	Severity Definitions		
	0	1	2
Erosion/ ulceration	None	Erosion	Ulceration

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, PhD
Date: 10/4/2010

Statistical Team Leader: Mohamed Alosh, PhD

cc:
DDDP/Walker
DDDP/Lindstrom
DDDP/Lolic
DDDP/Rashid
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Fritsch

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHLEEN S FRITSCH
10/04/2010

MOHAMED A ALOSH
10/04/2010
Concur with the primary reviewer's comments and conclusion.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 201153 **Applicant:** Graceway **Stamp Date:** 2/8/2010

Drug Name: Zyclara (imiquimod) cream 3.75% **NDA/BLA Type:** 505(b)(1) **Indication:** Genital warts

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Index and reference links are sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?
Yes.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Requests to the Applicant for the 74-day letter are listed here.
None.

Primary Statistical Reviewer: Kathleen Fritsch, PhD
Date: 4/7/2010

Statistical Team Leader: Mohamed Alosh, PhD

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICALS LLC	Zyclara (Imiquimod) Cream 3.75%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHLEEN S FRITSCH
04/07/2010

MOHAMED A ALOSH
04/07/2010
Concur with the review