CLINICAL REVIEW

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Dosing Regimen	Three times weekly
Indication	Molluscum Contagiosum
Intended Population	Children 2-12 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Aldara (imiquimod cream, 5%) is approved for use in children 12 years and older for the treatment of external genital/perianal warts with 3 times per week application for up to 16 weeks. Children below the age of 12 are treated off-label with Aldara for various skin disorders, including molluscum contagiosum (MC). To obtain safety and efficacy data for the treatment of MC in children, the FDA has issued a Written Request (Section 505A of the Federal Food, Drug, and Cosmetic Act) for evaluation of imiquimod for the treatment of MC in children 2-12 years of age. Three studies were requested, two independent, double-blind, vehicle-controlled safety and efficacy studies and one pharmacokinetic (PK) study. The studies were conducted according to the terms of the Written Request and Pediatric Exclusivity was granted by the Agency on December 13, 2006.

Efficacy was not demonstrated with 3 times per week topical application for up to 16 weeks in either of two independent phase 3 studies for the indication of MC in pediatric subjects 2-12 years of age. This reviewer recommends revision to package insert to include the findings from these two phase 3 clinical studies as well as the results of the PK study. The sponsor is not pursuing efficacy claims regarding MC, and this reviewer recommends revision to package insert to reflect that the treatment of MC is a limitation of use based on the negative results of these studies.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activity is needed other than revision of the package insert.

1.2.2 Required Phase 4 Commitments

No phase 4 commitments are indicated on the basis of this labeling supplement.

1.2.3 Other Phase 4 Requests

No other phase 4 requests are indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The clinical program included a phase 2 study, Study 1490-IMIQ, and two phase 3 studies, 1494-IMIQ and 1495-IMIQ, all in pediatric patients ages 2-12 years with MC. The two phase 3 study protocols were very similar, and for practical purposes related to this review are considered identical. Both phase 3 studies included three times weekly dosing for up to 16 weeks. The phase 2 study included daily dosing (7 days per week) for up to 8 weeks.

1.3.2 Efficacy

This labeling supplement contains the reports of two phase 3, multicenter, randomized, vehicle-controlled clinical studies in pediatric subjects 2-12 years of age. Complete clearance of all MC lesions at Week 18 was the primary clinical endpoint in both phase 3 studies. The subset of subjects with periocular MC also failed to show any trend of treatment benefit. In 1494-IMIQ, the complete clearance rate was 24% (52/217) in the Aldara Cream group compared with 26% (28/106) in the vehicle group. In 1495-IMIQ, the clearance rates were 24% (60/253) in the Aldara Cream group compared with 28% (35/126) in the vehicle group. These studies failed to demonstrate efficacy.

1.3.3 Safety

In the combined phase 3 study data, the most frequently reported possibly or probably related adverse event (AE) was application site reaction; 31% (144/470) of Aldara-treated subjects and 20% (47/232) of vehicle-treated subjects reported at least one application site reaction. Nine subjects discontinued a study due to an AE; 6 Aldara-treated subjects and 3 vehicle-treated subjects. The most common adverse events were application site reactions.

Local skin reactions (LSR) were recorded separately from adverse events. The most frequently recorded investigator-assessed LSR was erythema, where 93% (426/460) of imiquimod and 87% (195/223) of vehicle-treated subjects experienced erythema (any severity). A total of 73% (336/460) of imiquimod and 55% (122/223) of vehicle subjects had moderate or severe erythema at least once after treatment initiation. This is in keeping with the known local reaction profile of Aldara from use in other indications.

In the subgroup of subjects with periocular MC, erythema was the most frequently reported LSR. Fifty percent of subjects reported mild/moderate erythema as the most intense LSR in the periocular region during the study (no severe erythema was reported). Flaking/scaling/dryness was the second most frequently reported LSR, with 31% of subjects reporting. One severe LSR was reported in the periocular region in one patient (severe flaking/scaling/dryness). The remainder of LSR in the periocular region were either mild or moderate in maximum intensity.

In the phase 3 studies, the investigator could prescribe a rest period if the subject experienced signs or symptoms at the treatment site that restricted their daily activities or made continued application of the study cream difficult. In Study 1494, the 9% (19/217) of Aldara-treated subjects took a rest period compared with 4% (4/106) vehicle-treated subjects. In Study 1495, 6% (15/253) of Aldara-treated subjects took a rest period compared to 2% (2/126) of vehicle-treated subjects.

In the phase 3 studies, a subgroup of patients had hematologic assessments at baseline and following the end of treatment. A higher incidence rate of shift from normal WBC at baseline to below normal after the end of treatment in white blood cell (WBC) parameters in the imiquimod group was observed compared with vehicle control. In the Aldara group 13% (10/79) had a decrease from normal to below normal WBC count compared to 7% in vehicle (3/42). For absolute neutrophil counts, 12% of Aldara patients (9/78) and 5% of vehicle-treated patients (2/41) had decrease from normal to below normal. In the PK study where the drug was studied under maximum use conditions (minimum body surface area treated was 10%), 8 of 20 Aldara-treated subjects experienced shifts from normal to below normal absolute WBC count and 5 of 20 experienced shifts from normal to below normal absolute neutrophil counts. In this study, the median WBC count decreased by $1.4*10^9$/L and the median absolute neutrophil count decreased by $1.42*10^9$/L. The time to resolution of the low WBC parameters was not studied. It is possible that these findings may be due to systemic effects of imiquimod.

Other safety findings from the clinical trials included a higher rate of lymphadenopathy in the imiquimod group compared with control. While the difference between treatment groups overall was modest, 3% (14/470) in the Aldara group compared with 2% (5/232) in the vehicle group, the difference between treatment groups was highest in the <4 years of age subgroup, where the incidence rate was 7% (8/124) in the Aldara group compared with 0% (0/57) in the vehicle group.

Safety findings from spontaneous reports have included several unlabeled adverse reactions. A search of the AERS database revealed nine cases of erythema multiforme occurring in adult patients and four of the nine cases involved hospitalization. Another safety finding included a case of Henoch-Schonlein purpura in a 3 year-old boy treated for MC with Aldara. Finally, a case of treatment-emergent idiopathic thrombocytopenic purpura was reported in a child who had been receiving Aldara for MC. It is recommended that these adverse reactions be described in labeling.

1.3.4 Dosing Regimen and Administration

The dosing regimen studied in the clinical trials was 3 doses per week topically to skin affected by MC for up to 16 weeks (48 doses), stopping prior to 16 weeks of treatment if the investigator determined the subject was completely clear of MC lesions. Subjects weighing <25 kg were to apply up to 2 packets per dose application while subjects weighing ≥25 kg could apply up to 3 packets per dose application. Each packet contains 250 mg of cream, or 12.5 mg imiquimod.

1.3.5 Drug-Drug Interactions

No formal drug-drug interaction studies were done as part of this clinical development program and none are needed.

1.3.6 Special Populations

These studies were carried out under a pediatric Written Request and the Agency has granted the sponsor's request for pediatric exclusivity.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The drug product used in the studies was the currently marketed product, Aldara™ (imiquimod) Cream, 5%.

2.2 Currently Available Treatment for Indications

MC is a common childhood viral infection with cutaneous manifestations characterized by firm, umbilicated dome-shaped papules. Patients typically present with multiple MC lesions. The trunk, axillae, antecubital and popliteal fossae, and crural folds are frequently involved. MC can also occur on the eyelid and around the mouth, and ocular MC can induce conjunctivitis.

Currently, there are no FDA-approved drug therapies for the treatment of MC. Treatment options include watchful waiting, physical ablation (e.g., curettage, liquid nitrogen) and chemical ablation. MC lesions, typically resolve without treatment in immunocompetent patients. However, some lesions can take years to spontaneously clear and the virus can spread to other areas in the same patient as well as to other individuals.

2.3 Availability of Proposed Active Ingredient in the United States

Aldara is licensed in the United States and is indicated for the topical treatment of:

- Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults;
- Biopsy-confirmed, primary superficial basal cell carcinoma in immunocompetent adults; maximum tumor diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured; and
- External genital and perianal warts/condyloma acuminata; 12 years old and above.

2.4 Important Issues With Pharmacologically Related Products

The reviewer is not aware of pharmacologically related products.

2.5 Presubmission Regulatory Activity

Aldara was approved for the treatment of external genital and perianal warts in adults on February 27, 1997. On September 3, 2002, approval was granted for treatment of external genital and perianal warts in patients down to 12 years of age. On December 18, 2003, a

Pediatric Written Request (PWR) was issued by the Agency requesting pediatric studies (two safety and efficacy studies and a pharmacokinetic study) for imiquimod cream in treatment of MC in patients 2-12 years of age. The combined phase 3 studies would include at least 25 subjects with periocular MC to assess the safety of treatment of periocular lesions with imiquimod. On December 19, 2003, the sponsor submitted the protocols for two phase 3 safety and efficacy studies for treatment of MC in pediatric patients 2-12 years. A teleconference was held with 3M on February 5, 2004 in which agreements regarding the following points of the phase 3 study design were made.

- The sponsor agreed to submit a request for revised PWR with subject evaluations at weeks 2, 4, 8, 12 and 16 during dosing, but not limited to those time frames.
- The last dosing/application was at week 16. The Agency recommended a single timepoint for the efficacy endpoint at week 17 or 18 to prevent potential local reactions from study drug from obscuring the endpoint evaluation.
- The Agency recommend including assessments of ocular function in the clinical protocol.
- The age group for Studies 1 and 2 and the percentage for patients under 6 years of age were also to be addressed in a planned request for a revised PWR.

In subsequent communications with the Agency, the sponsor agreed that the age distribution of the children enrolled would include at least 50% of subjects under 6 years of age and at least 20% under 4 years of age.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No CMC data was submitted as part of this supplement and none was deemed necessary.

3.2 Animal Pharmacology/Toxicology

No animal pharmacology/toxicology data was submitted as part of this supplement and none was deemed necessary.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of clinical data in this supplement review included the two phase 3 study reports submitted in the application as well as clinical datasets and clinical photography of patients with periocular MC lesions.

4.2 Table of Clinical Studies

Table 1 Table of Clinical Studies in Molluscum Contagiosum

Study Number	Study Phase	Type of Study	Population	Patient Numbers Planned/Enrolled	Study Dates
1490-IMIQ	2	Randomized, double-blind, vehicle controlled, multicenter	Ages 2-12; MC	120/ 125	Nov 2003-Jan 2005
1494-IMIQ	3	Randomized, double-blind, vehicle controlled, multicenter	Ages 2-12; MC	300/ 323	Feb 2004-May 2005
1495-IMIQ	3	Randomized, double-blind, vehicle controlled, multicenter	Ages 2-12; MC	300/ 379	Jan 2004-May 2005
1498-IMIQ	1	Pharmacokinetic study	Ages 2-12; MC	15/ 22	Jul 2004-April 2006

4.3 Review Strategy

The two phase 3 studies were reviewed for both safety and efficacy in the treatment of MC. In addition, safety findings from the phase 2 clinical study were conceptually integrated with those of the two phase 3 studies.

4.4 Data Quality and Integrity

The data quality and integrity were adequate to allow substantive review.

4.5 Compliance with Good Clinical Practices

The sponsor submitted that each of the clinical studies were conducted in compliance with the Code of Federal Regulations of the USFDA and ICH E6, Guideline for Good Clinical Practices.

4.6 Financial Disclosures

The sponsor provided financial disclosure and none raised concerns.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Systemic absorption of imiquimod 5% cream across the affected skin of 22 patients aged 2 to 12 years with extensive MC lesion treatment area(s) involving at least 10% of the total body surface area (BSA) was observed at a dosing frequency of 3 applications per week for 4 weeks. Up to 3 packets of imiquimod were applied at each dose. The investigator determined the appropriate amount of study cream to administer per dose, based on each subject's weight and extent of

disease. Subjects who weighed ≤ 25 kg applied 1 or 2 packets of imiquimod cream, 5%; while subjects who weighed >25 kg applied 1 to 3 packets.

Pharmacokinetic measurements consisted of serum drug concentration measurements of imiquimod and 2 metabolites (S-26704/S-27700) after doses 1 and 12 (final dose) to calculate the Cmax, Tmax, and AUC after single and multiple doses. The primary analyte was serum imiquimod, and the primary PK variables were Cmax and AUC.

The main noteworthy findings and conclusions are summarized below. Please see PK review by Dr. Tapash for a full description of the study.

- Of the 22 subjects, nine were 5 years of age and under and thirteen were over the age of 5 years (range: 2-12 years). The median weight was 24.5 kg (range:14 kg- 47 kg). The median body surface area involvement at baseline was 13.5% (range: 10% - 23%).
- The highest systemic absorption was observed in a 2-year old girl (No. 0004/0051) with 14% BSA involvement who applied 2 packets per dose. At 8 hours following administration of the last dose, this patient had the highest concentration serum of imiquimod, 9.66 ng/mL, as well as imiquimod metabolites, 0.230 ng/mL. This information will be reported in the revised label to caution prescribers that young skin may show relatively high systemic exposure.
- When stratified by age, systemic exposure to imiquimod tended to be higher in 2- to 5-year old subjects than in 6- to 12-year old subjects, with the highest exposure in the 2- to 5-year old group administered 2 packets of cream (AUC=7 ng*hr/mL). This patient was reported to have the following treatment emergent adverse events: Streptococcal pharyngitis, application site reactions of redness and bleeding, and nervousness. It is possible that the application site reaction as well as the relatively large surface area (14%) compared to body mass (13.5 kg) may have led to the high serum levels of study drug.
- Decreases in some WBC parameters were observed in some subjects. Specifically, 5 patients experienced shifts from normal to below normal absolute neutrophil counts, 2 patients experienced normal to below normal lymphocyte counts and 8 patients experienced shifts from normal to below normal total WBC. These changes were not considered clinically significant by the investigators or the sponsor.
- Among the 20 patients with evaluable laboratory assessments, the median WBC count decreased by $1.4*10^9$/L and the median absolute neutrophil count decreased by $1.42*10^9$/L.
- There were no deaths or SAEs reported in the study. Of the 22 patients, the most frequently reported adverse events were application site reactions in 12 patients, fever in 3 patients, coughing in 3 patients, pharyngitis in 3 patients, and lymphadenopathy in 3 patients. A single severe AE was reported in one subject, fever. One subject experienced hypopigmentation at the target site post-treatment. One subject experienced an exacerbation of atopic dermatitis and was included under application site reaction. None of the patients discontinued during the study. During the study, Patient 1498/001/001 experienced bilateral wheezing (bronchospasm) and Patient 1498/006/0076 was diagnosed with a pneumonia which required therapy. The latter patient also experienced treatment emergent low WBC and neutrophil counts (WBC 4.4, absolute PMN 1.28).

- Local skin reactions were described separately from adverse events. Erythema was the most frequent local skin reaction (20/22). In 2 patients, the erythema was graded as severe. Flaking/scaling dryness was reported in 16/22 patients, and 14/22 patients had scabbing crusting.
- None of the 22 subjects enrolled in this study completely cleared their MC lesions during the study.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

6.1.1 Methods

Two randomized, multicenter, double-blind, vehicle-controlled studies were conducted in pediatric subjects ages 2-12, inclusive.

6.1.2 General Discussion of Endpoints

The primary efficacy parameter was complete clearance of all MC lesions (complete clinical resolution) from treatment initiation to the week 18 efficacy visit and was measured 2 weeks after the end of dosing period to prevent unblinding and allow assessment of complete resolution.

Secondary efficacy parameters included partial clearance, defined as ≥50% reduction from the baseline lesion count, and the and the change in total lesion count. Time-to-complete clearance was also measured.

6.1.3 Study Design

As stated earlier in this review, the two Phase 3 clinical trials were of similar design. Eligible subjects were 2 to 12 years old and had ≥ 2 clinically verified MC lesions (at least half had ≥5 lesions) not located on buttocks, or inguinal region or on hands only.

Subjects were randomly assigned to a treatment arm in blocks of 6 according to a computer-generated randomization schedule. Randomization was 2:1 (active:vehicle) for a planned number of 300 subjects to be randomized into the study. 3M Pharmaceuticals monitored the overall enrollment to ensure that ≥50% of the enrolled subjects had ≥5 MC lesions with no upper limit of the number of lesions; ≥ 50% of subjects were <6 years of age; ≥ 20% of subjects were < 4 years of age, and to ensure that a sufficient number of subjects had periocular MC lesions.

In both phase 3 studies, subjects applied 3 doses per week topically to skin affected by MC for up to 16 weeks (48 doses), stopping prior to 16 weeks of treatment if the investigator determined the subject was completely clear of MC lesions. Subjects weighing <25 kg were to apply up to 2

packets per dose application while subjects weighing ≥25 kg could apply up to 3 packets per dose application. Each packet contains 250 mg of cream, or 12.5 mg imiquimod.

MC lesions and application area locations were recorded on a provided body diagram. Clinic visits were scheduled at weeks 2, 4, 8, 12, and 16, as well as posttreatment at weeks 18 and 28. At each study visit, MC lesions were counted and recorded, and safety procedures were performed. Subjects returned at week 18 for the primary efficacy and post-treatment safety assessments. All subjects were to report to the clinic at week 28 for final safety and efficacy assessments.

The primary dataset analyzed for efficacy and safety was the intent-to-treat (ITT) dataset, consisting of all randomized subjects. Comparisons between treatment groups of the primary efficacy variable (complete clearance rate at the week 18 study visit) were by the Cochran-Mantel-Haenzsel (CMH) Test stratified on pooled center.

6.1.4 Efficacy Findings

The two phase 3 randomized, vehicle-controlled, double-blind trials involved 702 pediatric patients with molluscum contagiosum (470 exposed to Aldara; median age 5 years, range 2-12 years). The median number of baseline lesions was 17 in Study 1494 and 15 in Study 1495.

The analyses of the primary endpoint, complete clearance rates at Week 18 (2 weeks post-treatment), are presented in the following table. Efficacy was not established in these studies.

Table 2 Complete Clearance Rate for Molluscum Contagiosum at Week 18

Study	Aldara Cream	Vehicle
1494	24% (52/217)	26% (28/106)
1495	24% (60/253)	28% (35/126)

In both studies, 24% of Aldara treated patients experienced complete clearance compared with 26% and 28% in Vehicle-treated patients, in Studies 1494 and 1495, respectively.

(b) (4)

6.1.5 Efficacy Conclusions

Neither of the phase 3 clinical studies demonstrated efficacy of Aldara for the treatment of MC. The response rate was numerically higher in the vehicle-treated arms in both studies compared with the Aldara group.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths reported in any of the clinical studies.

7.1.2 Other Serious Adverse Events

In Study 1494, there were 5 SAEs reported by 3 subjects (1 vehicle and 2 were imiquimod). The SAEs were considered by the investigator to be not related to study cream. In Study 1495, there was one SAE reported in 1 subject who received imiquimod cream and none in vehicle.

Table 4 Serious Adverse Events in Studies 1494 and 1495

Study	SAE	Demographics	Onset day	Outcome	Relationship to study treatment/ investigator	Action with respect to study drug	Severity
Vehicle							
1494	Asthma	9 y/o, Caucasian female		Recovered	NR	Completed treatment	Severe
Imiquimod							
1494	Broken left humerus (secondary to a fall)	5 y/o, Caucasian female	25	Recovered	NR	Completed treatment	Moderate
1494	Encephalopathy (anoxic brain injury/encephalopathy)	7 y/o, Caucasian female	67	Persistent	NR	Discontinued	Severe
	Inflicted Injury (cutting of throat)		67	Recovered	NR		Severe
	Inflicted injury s/p penetrating neck injury		67	Persistent	NR		Severe
1495	Ear ache	5 y/o, Caucasian female				Discontinued, lost to follow-up	Moderate
	Fever			Recovered	NR		Mild
	Sore throat serious			Recovered	NR		Moderate
	Emesis				NR		

Reviewer's comment: This reviewer agrees with the investigator's assessment that these serious adverse events are not related to the use of study drug.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The following table shows study discontinuations in the combined studies and does not include treatment interruptions (See section 7.1.3.3).

Table 5 Discontinuations During the Treatment Period in the Combined Phase 3 Studies

Primary Reason for Discontinuation	Imiquimod (n=470)	Vehicle (n=232)
Total	64 (14%)	37 (16%)
Adverse Event	5 (1%)	2 (1%)
Lost to Follow-up	38 (8%)	18 (8%)
Personal	11 (2%)	8 (3%)
Lack of Therapeutic Effect	6 (1%)	7 (3%)
Other	3 (1%)	2 (1%)
Local skin reaction/sign	1 (<1%)	0 (0%)

Overall, 14% (64/470) and 16% (37/226) of imiquimod and vehicle subjects, respectively, discontinued from the 16-week treatment period. The most common reason for discontinuation in each treatment group was "lost to follow-up" which accounts for 8% of subjects discontinuing in the Aldara group and vehicle group, respectively.

7.1.3.2 Adverse events associated with dropouts

All randomized subjects were expected to complete posttreatment visits even if they did not complete the treatment period. Subjects who discontinued during the treatment period were asked to return for their posttreatment assessments. Therefore, a subject could discontinue from a study during the treatment period, the posttreatment period, or both. In the combined studies, 1.3% imiquimod subjects (6/470) discontinued during the treatment period due to AEs or LSRs (see table 4).

Table 6 Discontinuations Due to Adverse Events or Local Skin Reactions.

Study No.	Subject No.	Study Cream	Primary Reason for Discontinuation[a]	Intensity/ Relationship	Action Taken / Outcome	Discontinuation Period	Comments
1494-IMIQ	0002/0208	Imiquimod	Application site reaction (AE)	Moderate / probably related	Required therapy, study cream stopped / recovered	Treatment	Bleeding due to scratched perioral lesion (treatment area)
	0009/0144	Vehicle	Rash erythematous (AE)	Mild/ possibly related	Study cream stopped / recovered	Treatment and posttreatment	Exanthem on chest, abdomen, and back (some in treatment area)
	0020/0105	Imiquimod	Inflicted injury (SAE)	Severe / not related	Required therapy, study cream stopped / recovered	Posttreatment	Cutting of throat
			Inflicted injury (SAE)	Severe / not related	Required therapy, study cream stopped / persistent		Status post penetrating neck injury including injury to right lobe of thyroid gland and right internal jugular vein
			Encephalopathy	Severe / not related	Required therapy, study cream stopped / persistent		Anoxic brain injury
	0021/0032	Imiquimod	Application site reaction (AE)	Moderate / probably related	Study cream stopped / persistent	Treatment and posttreatment	Pain in left axilla (treatment area)
1495-IMIQ	0011/0513	Vehicle	Application site reaction (AE)	Moderate / possibly related	Required therapy, study cream stopped / recovered	Treatment	Generalized discomfort in all treatment areas
			Application site reaction (AE)	Moderate / possibly related	Required therapy, study cream stopped / recovered		Impetigo in treatment area (popliteal area)

Discontinuations Due to Adverse Events or Local Skin Reactions (continued)

Study No.	Subject No.	Study Cream	Primary Reason for Discontinuation[a]	Intensity/ Relationship	Action Taken / Outcome	Discontinuation Period	Comments
1495-IMIQ	0012/0586	Imiquimod	Application site reaction (AE)	Moderate / possibly related	Study cream stopped/ persistent	Treatment and posttreatment	Eczema (treatment area)
	0018/0561	Imiquimod	Application site reaction (AE)	Moderate / possibly related	Study cream stopped / persistent	Treatment and posttreatment	Ulcerated area (treatment area)
	0018/0838	Imiquimod	Application site reaction (AE)	Mild / possibly related	Study cream stopped / recovered	Treatment and posttreatment	Skin roughness (treatment area)
	0019/0530	Imiquimod	LSR	Moderate (erythema, edema) Mild (scabbing / crusting)	Discontinued from study, study cream stopped / NA	Treatment and posttreatment	NA
	0022/0483	Vehicle	Application site reaction (AE)	Moderate / probably related	Required therapy/ persistent	Posttreatment	Infected molluscum on right leg (treatment area)

7.1.3.3 Other significant adverse events (dose reduction resulting from adverse events)

In the phase 3 studies, the investigator could prescribe a rest period if the subject experienced signs or symptoms at the treatment site that restricted their daily activities or made continued application of the study cream difficult.

In Study 1494, the 9% (19/217) of Aldara-treated subjects took a rest period compared with 4% (4/106) vehicle-treated subjects. Of the 19 Aldara-treated subjects who took a rest period(s), the median number of doses withheld was 3 doses (range, 1 to 20) and the median first week that a rest period was taken was week 5 (range, 1 to 13). Of these subjects, all but one resumed treatment by week 16.

In Study 1495, 6% (15/253) of Aldara-treated subjects took rest period(s) compared to 2% (2/126) of vehicle-treated subjects. Of the 15 Aldara-treated subjects who took a rest period(s), the median number of doses withheld was 3 doses (range, 1 to 6) and the median first week that a rest period was taken was week 6 (range, 3 to 11). All 15 Aldara-treated subjects resumed dosing after their last rest period.

7.1.4 Other Search Strategies

No other search strategies were used in this review.

7.1.5 Common Adverse Events

Local skin reactions (LSR) were actively assessed and recorded separately from adverse events. The maximum observed intensity of LSR across study visits are summarized in the following table. The most frequently recorded investigator-assessed LSR was erythema, where 93% (426/460) of imiquimod-treated and 87% (195/223) of vehicle-treated subjects experienced erythema (any severity). A total of 73% (336/460) of imiquimod-treated and 55% (122/223) of vehicle-treated subjects had moderate or severe erythema at least once after treatment initiation. This is in keeping with the known local reaction profile of Aldara from use in other indications.

Table 7 Local Skin Reactions During Treatment by Maximum Intensity (Combined Phase 3 Studies)

Type of Reaction	Intensity	Imiquimod (n=460)		Vehicle (n=223)	
Erythema	None	34	(7%)	28	(13%)
	Mild	90	(20%)	73	(33%)
	Moderate	208	(45%)	101	(45%)
	Severe	128	(28%)	21	(9%)
Edema	None	171	(37%)	104	(47%)
	Mild	123	(27%)	66	(30%)
	Moderate	128	(28%)	48	(22%)
	Severe	38	(8%)	5	(2%)
Erosion/Ulceration	None	310	(67%)	187	(84%)
	Mild	86	(19%)	27	(12%)
	Moderate	53	(12%)	9	(4%)
	Severe	11	(2%)	0	(0%)
Weeping/Exudate	None	389	(85%)	208	(93%)
	Mild	50	(11%)	13	(6%)
	Moderate	14	(3%)	2	(1%)
	Severe	7	(2%)	0	(0%)
Flaking/Scaling/Dryness	None	161	(35%)	113	(51%)
	Mild	133	(29%)	72	(32%)
	Moderate	142	(31%)	37	(17%)
	Severe	24	(5%)	1	(<1%)
Scabbing/Crusting	None	158	(34%)	108	(48%)
	Mild	154	(34%)	74	(33%)
	Moderate	126	(27%)	39	(18%)
	Severe	22	(5%)	2	(1%)

In the subgroup of subjects with periocular MC, erythema was the most frequently reported LSR (see Table 8). Fifty percent of subjects reported mild/moderate erythema as the most intense LSR in the periocular region during the study (no severe erythema was reported).

Flaking/scaling/dryness was the second most frequently reported LSR, with 31% of subjects reporting. One severe LSR was reported in the periocular region in one patient (severe flaking/scaling/dryness). The remainder of LSR in the periocular region were either mild or moderate in maximum intensity.

Table 8 Most Intense Reactions in the Periocular Region (Combined Phase 3 Studies)

Type of Reaction	Intensity	Imiquimod 3x/Week (n=36)	Vehicle 3x/Week (n=23)
Erythema	None/Not Present	18 (50.0%)	16 (69.6%)
	Mild	12 (33.3%)	7 (30.4%)
	Moderate	6 (16.7%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)
Edema	None/Not Present	28 (77.8%)	20 (87.0%)
	Mild	5 (13.9%)	3 (13.0%)
	Moderate	3 (8.3%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)
Erosion/Ulceration	None/Not Present	34 (94.4%)	23 (100.0%)
	Mild	2 (5.6%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)
Weeping/Exudate	None/Not Present	36 (100.0%)	23 (100.0%)
	Mild	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)
Flaking/Scaling/Dryness	None/Not Present	25 (69.4%)	22 (95.7%)
	Mild	10 (27.8%)	1 (4.3%)
	Moderate	0 (0.0%)	0 (0.0%)
	Severe	1 (2.8%)	0 (0.0%)
Scabbing/Crusting	None/Not Present	28 (77.8%)	20 (87.0%)
	Mild	7 (19.4%)	3 (13.0%)
	Moderate	1 (2.8%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were elicited from either the subject or their legal custodian using a non-directive approach at each office visit.

During the treatment period, investigators performed directed assessment of the treatment area for the following types of local skin reactions: Erythema, Edema, Erosion/Ulceration, Weeping/Exudate, Flaking/Scaling/Dryness and Scabbing/Crusting. These were assessed on a 4-point scale 0=none; 1=mild; 2= moderate and 3=severe.

At the end-of-treatment visit, week 18/efficacy assessment visit, and the week 28/end-of study

visit, the investigators performed skin quality assessments of each application area. The following characteristics were graded on the same 4-point scale:

· Hyperpigmentation (independent of texture change or hypopigmentation)
· Hypopigmentation (independent of texture change or hyperpigmentation)
· Degree of scarring (texture change independent of pigmentary changes)
· Atrophy

The investigators were to also count the number of pits (hollow depressions in each application area at the week 18/efficacy assessment visit and at the week 28/end-of-study visit.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Treatment emergent adverse events were summarized by the World Health Organization's preferred terms and body systems, as modified by 3M Pharmaceuticals.

Reviewer's comment: The sponsor did not explain what modifications 3M made to the WHO preferred terms and body systems. Some areas were unclear. For example, rhinitis was listed under respiratory system disorders as well as under resistance mechanism disorders (in cases where it was thought to be allergic in nature). There was a section called "secondary terms" under body system category. In this section was varicella, post-operative pain, abrasion, bite, inflicted injury, and molluscum contagiosum. It is not clear why varicella was not included under resistance mechanism disorders along with other viral infections. The reviewer reclassified the adverse event as infectious.

7.1.5.3 Incidence of common adverse events

In both phase 3 clinical studies combined, 67% (317/470) imiquimod-treated patients experienced at least one adverse event compared with 70% (162/232) of vehicle-treated patients. In both phase 3 clinical studies, the most commonly reported AEs were application site reactions. Application site reactions were reported in 33% (157/470) imiquimod-treated patients and 22% (52/232) vehicle-treated patients.

7.1.5.4 Common adverse event tables

Table 9 AEs at least 1% in any treatment group and not higher in Vehicle

AE Body System	WHO Term	Active N=470		Vehicle N=232	
Application Site		%	n	%	n
	Application Site Reaction	33	157	22	52
Body as a Whole- General					
	Fever	10	48	10	23
Central & Peripheral Nervous System					
	Headache	3	16	3	6
Gastro-Intestinal System					
	Dyspepsia	2	9	1	3
	Gastroenteritis	2	11	2	4
Musculoskeletal System					
	Myalgia	1	5	0	0
Resistance Mechanism					
	Infection Viral	2	8	1	2
	Otitis Media	5	24	3	7
Respiratory System					
	Asthma	1	5	1	3
	Coughing	12	57	11	26
	Pharyngitis	5	25	5	12
	Pulmonary Congestion	1	6	1	3
	Rhinitis	13	61	11	25
Skin and Appendages					
	Dermatitis	3	15	1	3
	Eczema	3	14	2	5
	Pruritus	2	7	<1	1
	Rash	3	16	2	5
	Skin Disorder	2	11	2	5
Vision Disorders	Conjunctivitis	3	16	2	5
White Cell and Reticular	Lymphadenopathy	3	14	2	5

Excludes secondary terms: “abrasion nos” and “bite”

7.1.5.5 Identifying common and drug-related adverse events

Local skin reactions are the most common of the drug-related adverse events observed with Aldara therapy. The phase 3 clinical studies included directed assessment of the following types of local skin reactions: Erythema, Edema, Erosion/Ulceration, Weeping/Exudate, Flaking/Scaling/Dryness and Scabbing/Crusting. These were assessed on a 4-point scale 0=none; 1=mild; 2= moderate and 3=severe. The following tabulations show the percentage of subjects by highest grade of severity for each of the following local skin reactions. For each of the local reaction categories, the spectrum of severity is shifted towards higher severity in the Aldara group compared with vehicle. The percentage of Aldara-treated subjects with a grade of 'severe' is consistently higher compared with the vehicle group, and the percentage with 'none' as the highest rating is consistently lower compared with the vehicle group.

Table 10 Erythema

Grade	Aldara N=460	Vehicle N=223
none	7%	13%
mild	20%	33%
moderate	45%	45%
severe	28%	9%

Table 11 Erosion-Ulceration

Grade	Aldara N=460	Vehicle N=223
none	67%	84%
mild	19%	12%
moderate	12%	4%
severe	2%	0%

Table 12 Edema

Grade	Aldara N=460	Vehicle N=223
none	37%	47%
mild	27%	30%
moderate	28%	22%
severe	8%	2%

Table 13 Scabbing-Crusting

Grade	Aldara N=460	Vehicle N=223
none	34%	48%
mild	33%	33%
moderate	27%	17%
severe	5%	1%

Table 14 Flaking-Scaling-Dryness

Grade	Aldara N=460	Vehicle N=223
none	35%	51%
mild	29%	32%
moderate	31%	17%
severe	5%	<1%

Table 15 Weeping-Exudate

Grade	Aldara N=460	Vehicle N=223
none	85%	93%
mild	11%	6%
moderate	3%	1%
severe	1-2%	0%

7.1.5.6 Additional analyses and explorations

The incidence rates of adverse events occurring in the combined phase 3 studies are shown in the following table.

Table 16 Adverse Events by Body System and WHO Term

AE Body System	WHO Term	Active N=470		Vehicle N=232	
		%	n	%	n
Application Site	Application Site Reaction	33.4	157	22.4	52
Body as a Whole - General	Allergic Reaction	0.2	1	1.3	3
	Face Edema	0	0	0.4	1
	Fatigue	0	0	0.4	1
	Fever	10.2	48	9.9	23
	Influenza-Like Symptoms	0.6	3	0.9	2
	Leg Pain	0.2	1	0.4	1
	Pain	0.4	2	0.4	1
	Pain Trauma Activated	0.2	1	0.4	1
Central & Peripheral Nervous System	Dizziness	0.2	1	0.4	1
	Encephalopathy	0.2	1	0	0
	Headache	3.4	16	2.6	6
	Hyperaesthesia	0.2	1	0	0
	Neuropathy	0.2	1	0	0
Collagen Disorders	Arthritis Rheumatoid	0	0	0.4	1
Gastro-Intestinal System	Abdominal Pain	0.4	2	0.4	1
	Cheilitis	0	0	0.4	1
	Constipation	0.4	2	1.7	4
	Diarrhea	2.8	13	4.3	10
	Dyspepsia	1.9	9	1.3	3
	Dysphagia	0	0	0.4	1
	Gastroenteritis	2.3	11	1.7	4
	Lip Disorder	0	0	0.4	1
	Nausea	0.6	3	0.4	1
	Stomatitis Ulcerative	0.4	2	0	0
	Tooth Ache	0.2	1	0.4	1
	Tooth Caries	0.2	1	0	0
	Tooth Disorder	0.2	1	0	0
	Vomiting	5.7	27	6.5	15

AE Body System	WHO Term	Active N=470		Vehicle N=232	
		%	n	%	n
Hearing and Vestibular	Ear Ache	1.5	7	1.7	4
	Ear Disorder NOS	0.6	3	0.4	1
Heart Rate and Rhythm Disorders	Bradycardia	0	0	0.4	1
Metabolic / Nutritional	Acidosis	0.2	1	0	0
	Dehydration	0.4	2	0	0
Musculoskeletal System	Back Pain	0.2	1	0.4	1
	Myalgia	1.1	5	0	0
	Tendon Disorder	0	0	0.4	1
Neoplasm	Neoplasm Nos	0	0	0.9	2
Platelet, Bleeding & Clotting	Epistaxis	0.6	3	0	0
	Purpura	0.2	1	0.4	1
Poison Specific Terms	Sting	0.2	1	0	0
	Anorexia	0	0	0.4	1
Psychiatric	Anxiety	0.2	1	0	0
	Concentration Impaired	0.2	1	0.9	2
	Depression	0	0	0.4	1
	Insomnia	0.2	1	0	0
	Nervousness	0.2	1	0	0
	Somnolence	0	0	0.4	1
	Anemia Hypochromic	0	0	0.4	1
Reproductive Disorders, Female	Dysmenorrhoea	0	0	0.4	1
	Leukorhea	0.2	1	0	0
Reproductive Disorders, Male	Hernia Inguinal	0.2	1	0	0
	Penis Disorder	0.2	1	0	0

AE Body System	WHO Term	Active N=470		Vehicle N=232	
		%	n	%	n
Resistance Mechanism	Abscess	0	0	1.3	3
	Allergic Reaction	0.2	1	0	0
	Herpes Simplex	0.6	3	0	0
	Infection	3.8	18	3.9	9
	Infection Bacterial	0.2	1	0.4	1
	Infection Parasitic	0.2	1	0	0
	Infection TBC	0.2	1	0	0
	Infection Viral	1.7	8	0.9	2
	Otitis Media	5.1	24	3.0	7
	Pharyngitis	0.4	2	0	0
	Pneumonia	0	0	0.4	1
	Rhinitis	2.8	13	0.9	2
	Upper Resp Tract Infection	4.9	23	5.6	13
	Varicella	0.4	2	0	0
Respiratory System	Asthma	1.1	5	1.3	3
	Bronchitis	0.9	4	0.9	2
	Bronchospasm	0.9	4	0	0
	Coughing	12.1	57	11.2	26
	Pharyngitis	4.9	23	5.2	12
	Pneumonia	0.6	3	2.2	5
	Pulmonary Congestion	1.3	6	1.3	3
	Respiratory Disorder	0.2	1	0.4	1
	Rhinitis	10.2	48	9.9	23
	Sinusitis	3.6	17	4.7	11
	Stridor	0.9	4	0	0
	Upper Resp Tract Infection	11.9	56	13.8	32
Secondary Terms	Abrasion Nos	1.3	6	0.9	2
	Bite	1.5	7	1.3	3
	Cyst Nos	0.2	1	0.4	1
	Inflicted Injury	3.6	17	4.7	11
	Molluscum Contagiosum	4.5	21	9.9	23
	Post-Operative Pain	0.6	3	0.9	2

AE Body System	WHO Term	Active N=470		Vehicle N=232	
		%	n	%	n
Skin and Appendages	Acne	0	0	0.4	1
	Bullous Eruption	0.4	2	0.4	1
	Burn	0.6	3	0.4	1
	Dermatitis	3.2	15	1.3	3
	Dermatitis Contact	0.9	4	0.9	2
	Dermatitis Fungal	0.4	2	0	0
	Dermatitis Lichenoid	0	0	0.4	1
	Eczema	3.0	14	2.2	5
	Erythema Multiforme	0	0	0.4	1
	Folliculitis	0.6	3	0	0
	Furunculosis	0.2	1	0.4	1
	Hyperkeratosis	0.6	3	0.9	2
	Ingrowing Nails	0.2	1	0	0
	Otitis Externa	0.4	2	1.3	3
	Perineal Pain Female	0.2	1	0	0
	Photosensitivity Reaction	0.9	4	0.9	2
	Pityriasis Rosea	0	0	0.4	1
	Pruritus	1.5	7	0.4	1
	Psoriasis	0.2	1	0	0
	Rash	3.4	16	2.2	5
	Rash Erythematous	1.1	5	2.2	5
	Rash Maculo-Papular	0	0	0.9	2
	Rash Pustular	0.2	1	.	.
	Skin Disorder	2.3	11	2.2	5
	Skin Dry	0.6	3	1.3	3
	Skin Exfoliation	0.2	1	0	0
	Skin Reaction Localized	0.2	1	0	0
	Skin Ulceration	0.2	1	0	0
	Sweat Gland Disorder	0.2	1	0.4	1
	Urticaria	0.9	4	0.9	2
	Verruca	0.9	4	1.3	3
Urinary System Disorders	Dysuria	0.2	1	0	0
	Micturition Frequency	0	0	0.4	1
	Pyelonephritis	0.2	1	0	0
Vision Disorders	Blepharitis	0	0	0.4	1
	Conjunctivitis	3.4	16	2.2	5
	Xerophthalmia	0	0	0.4	1
White Cell and Reticuloendothelial system	Lymphadenopathy	2.6	12	2.2	5
	Lymphadenopathy Cervical	0.4	2	0	0

The following shows the incidence of adverse events for subjects under the age of 4 in the combined phase 3 studies.

Table 17 Incidence of Adverse Events for Subjects <4 Years Old - ITT (Combined Phase 3 Studies)

Body System Preferred Term	Imiquimod (n=124)	Vehicle (n=57)
APPLICATION SITE DISORDERS	44 (35.5%)	13 (22.8%)
Application Site Reaction	44 (35.5%)	13 (22.8%)
Infection Bacterial	1 (0.8%)	0 (0.0%)
BODY AS A WHOLE - GENERAL DISORDERS	17 (13.7%)	8 (14.0%)
Allergic Reaction	1 (0.8%)	1 (1.8%)
Fatigue	0 (0.0%)	1 (1.8%)
Fever	16 (12.9%)	6 (10.5%)
Influenza-Like Symptoms	1 (0.8%)	0 (0.0%)
Pain	1 (0.8%)	0 (0.0%)
CENTRAL & PERIPHERAL NERVOUS SYSTEM	5 (4.0%)	0 (0.0%)
Headache	4 (3.2%)	0 (0.0%)
Hyperaesthesia	1 (0.8%)	0 (0.0%)
GASTRO-INTESTINAL SYSTEM DISORDERS	14 (11.3%)	8 (14.0%)
Abdominal Pain	1 (0.8%)	0 (0.0%)
Constipation	1 (0.8%)	1 (1.8%)
Diarrhea	3 (2.4%)	4 (7.0%)
Dyspepsia	2 (1.6%)	1 (1.8%)
Gastroenteritis	2 (1.6%)	0 (0.0%)
Stomatitis Ulcerative	1 (0.8%)	0 (0.0%)
Tooth Ache	0 (0.0%)	1 (1.8%)
Vomiting	7 (5.6%)	3 (5.3%)
MUSCULAR-SKELETAL SYSTEM DISORDERS	2 (1.6%)	0 (0.0%)
Myalgia	2 (1.6%)	0 (0.0%)
PLATELET,BLEEDING & CLOTTING DISORDERS	1 (0.8%)	0 (0.0%)
Purpura	1 (0.8%)	0 (0.0%)
PSYCHIATRIC DISORDERS	1 (0.8%)	1 (1.8%)
Anorexia	0 (0.0%)	1 (1.8%)
Nervousness	1 (0.8%)	0 (0.0%)
REPRODUCTIVE DISORDERS, MALE	2 (3.3%)	0 (0.0%)
Hernia Inguinal	1 (1.6%)	0 (0.0%)
Penis Disorder	1 (1.6%)	0 (0.0%)

(Continued next page)

Table 17 Incidence of Adverse Events for Subjects <4 Years Old - ITT (Continued)

Body System Preferred Term	Imiquimod (n=124)	Vehicle (n=57)
RESISTANCE MECHANISM DISORDERS	24 (19.4%)	6 (10.5%)
Abscess	0 (0.0%)	1 (1.8%)
Herpes Simplex	1 (0.8%)	0 (0.0%)
Infection	6 (4.8%)	3 (5.3%)
Infection Viral	3 (2.4%)	0 (0.0%)
Otitis Media	12 (9.7%)	2 (3.5%)
Pharyngitis	1 (0.8%)	0 (0.0%)
Rhinitis	4 (3.2%)	0 (0.0%)
Upper Resp Tract Infection	5 (4.0%)	1 (1.8%)
RESPIRATORY SYSTEM DISORDERS	50 (40.3%)	20 (35.1%)
Asthma	2 (1.6%)	1 (1.8%)
Bronchitis	3 (2.4%)	1 (1.8%)
Bronchospasm	1 (0.8%)	0 (0.0%)
Coughing	15 (12.1%)	7 (12.3%)
Laryngitis	1 (0.8%)	0 (0.0%)
Pharyngitis	2 (1.6%)	0 (0.0%)
Pneumonia	1 (0.8%)	1 (1.8%)
Pulmonary Congestion	2 (1.6%)	1 (1.8%)
Rhinitis	15 (12.1%)	6 (10.5%)
Sinusitis	5 (4.0%)	1 (1.8%)
Stridor	4 (3.2%)	0 (0.0%)
Upper Resp Tract Infection	24 (19.4%)	10 (17.5%)
SECONDARY TERMS	13 (10.5%)	12 (21.1%)
Abrasion Nos	1 (0.8%)	1 (1.8%)
Bite	2 (1.6%)	2 (3.5%)
Inflicted Injury	4 (3.2%)	4 (7.0%)
Molluscum Contagiosum	6 (4.8%)	5 (8.8%)
Post-Operative Pain	0 (0.0%)	1 (1.8%)
SKIN AND APPENDAGES DISORDERS	27 (21.8%)	8 (14.0%)
Bullous Eruption	1 (0.8%)	0 (0.0%)
Burn	1 (0.8%)	0 (0.0%)
Dermatitis	3 (2.4%)	0 (0.0%)
Dermatitis Contact	1 (0.8%)	0 (0.0%)
Dermatitis Fungal	1 (0.8%)	0 (0.0%)
Eczema	4 (3.2%)	1 (1.8%)
Erythema Multiforme	0 (0.0%)	1 (1.8%)
Folliculitis	2 (1.6%)	0 (0.0%)
Furunculosis	0 (0.0%)	1 (1.8%)
Hyperkeratosis	1 (0.8%)	0 (0.0%)
Photosensitivity Reaction	1 (0.8%)	1 (1.8%)
Rash	5 (4.0%)	0 (0.0%)

Rash Erythematous	1 (0.8%)	2 (3.5%)
Skin Disorder	4 (3.2%)	1 (1.8%)

Table 17 Incidence of Adverse Events for Subjects <4 Years Old - ITT (Continued)

Body System Preferred Term	Imiquimod (n=124)	Vehicle (n=57)
SKIN AND APPENDAGES DISORDERS (cont)		
Skin Dry	1 (0.8%)	0 (0.0%)
Skin Reaction Localized	1 (0.8%)	0 (0.0%)
Skin Ulceration	1 (0.8%)	0 (0.0%)
Sweat Gland Disorder	1 (0.8%)	1 (1.8%)
Urticaria	3 (2.4%)	1 (1.8%)
VISION DISORDERS	9 (7.3%)	2 (3.5%)
Conjunctivitis	9 (7.3%)	2 (3.5%)
WHITE CELL AND RES DISORDERS	8 (6.5%)	0 (0.0%)
Lymphadenopathy	7 (5.6%)	0 (0.0%)
Lymphadenopathy Cervical	1 (0.8%)	0 (0.0%)
Subjects Reporting at Least One Adverse Event	97 (78.2%)	37 (64.9%)
Subjects Reporting at Least One Adverse Event Excluding Application Site Reactions	86 (69.4%)	32 (56.1%)
Subjects Reporting at Least One Adverse Event Excluding Molluscum Contagiosum	96 (77.4%)	37 (64.9%)

Overall, a higher proportion of patients under the age of 4 years reported at least one adverse event in the imiquimod group compared with the vehicle group, 78% vs. 65%. Some adverse events that occurred with higher frequency in the active arm compared with vehicle included: application site reactions, headache, myalgia, otitis media, rhinitis, sinusitis, stridor, dermatitis, rash, conjunctivitis and lymphadenopathy.

7.1.6 Less Common Adverse Events

Less common adverse events included a case of pulmonary tuberculosis that was diagnosed in a 4 year –old girl in Study 1494 (004/0227). This event was not related to the investigational treatment per investigator and was not classified as a serious adverse event by the investigator or the by sponsor.

Also notable, was an event of moderate pyelonephritis in a 6-year-old girl (002/058) assigned to the Aldara group in Study 1494. The subject recovered. This was not classified as a serious adverse event by the investigator or by the sponsor.

Reviewer's comment: This reviewer agrees that these two infectious adverse events do not appear to plausibly related to study drug based on our knowledge of Aldara.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In the phase 3 clinical studies, blood sampling for hematology laboratory tests at the screening/initiation and end-of-treatment visits (at selected study centers from approximately 25% of all subjects enrolled).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Each baseline and end- of- treatment (EOT) result was classified as low, normal, or high, based on the reference range. A shift table of baseline vs. EOT results relative to the reference range was constructed by using 9 categories (low-low, low-normal, low-high, normal-low, normal-normal, normal-high, high-low, high-normal, high-high). The number of subjects within each category was displayed by treatment group for each laboratory test.

In addition to these analyses, all laboratory values falling outside the reference range were listed.

The following data handling rules applied to the analysis of laboratory data:
- For each subject, only EOT laboratory data collected within 7 days of the last application of study cream were included.
- If more than 1 baseline laboratory assessment was done for an individual subject, only values from the last baseline laboratory assessment were used.
- If more than 1 EOT laboratory assessment was done for an individual subject, only the values from the first EOT laboratory assessment were used.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The following table shows absolute values and changes from baseline for select laboratory parameters.

Table 18 Study 1494: Absolute Values and Changes from Baseline for Laboratory Parameters

Lab Parameter (Unit)	3x/Week Treatment	Visit	n	Mean	S.D.	Median	n Change	Mean Change	S.D. Change	Median Change
Platelets (X10*9/L)	Imiquimod	Baseline	70	312.2	71.96	305.5				
		EOT	38	332.9	73.97	324.0	36	15.17	56.20	11.00
	Vehicle	Baseline	42	322.4	62.63	318.0				
		EOT	27	323.7	74.03	318.0	25	3.08	71.37	-18.00
RBC (X10*12/L)	Imiquimod	Baseline	71	4.57	0.27	4.58				
		EOT	38	4.62	0.29	4.65	36	0.06	0.25	0.06
	Vehicle	Baseline	43	4.70	0.29	4.71				
		EOT	27	4.68	0.30	4.73	26	0.02	0.22	0.02
WBC (X10*9/L)	Imiquimod	Baseline	71	7.25	1.85	7.10				
		EOT	38	7.41	2.22	6.80	36	0.10	1.96	0.10
	Vehicle	Baseline	43	7.07	1.92	6.60				
		EOT	27	8.14	2.72	7.40	26	1.18	2.49	0.85
Neutrophils-AB (X10*9/L)	Imiquimod	Baseline	71	3.21	1.37	2.94				
		EOT	38	3.35	1.43	3.13	36	0.13	1.63	0.18
	Vehicle	Baseline	42	3.17	1.32	2.88				
		EOT	27	4.30	2.52	3.54	25	0.97	2.69	0.43

Table 19 Study 1495: Absolute Values and Changes from Baseline for Laboratory Parameters

Lab Parameter (Unit)	3x/Week Treatment	Visit	n	Mean	S.D.	Median	n Change	Mean Change	S.D. Change	Median Change
Platelets (X10*9/L)	Imiquimod	Baseline	53	313.4	65.52	315.0				
		EOT	45	327.9	84.59	315.0	40	14.83	56.74	4.50
	Vehicle	Baseline	26	325.4	79.27	320.0				
		EOT	16	345.7	72.18	347.0	15	19.20	53.34	15.00
RBC (X10*12/L)	Imiquimod	Baseline	54	4.59	0.54	4.68				
		EOT	47	4.74	0.31	4.73	43	0.13	0.56	0.03
	Vehicle	Baseline	27	4.72	0.41	4.64				
		EOT	16	4.73	0.35	4.76	16	0.10	0.32	0.04
WBC (X10*9/L)	Imiquimod	Baseline	54	7.09	1.90	6.85				
		EOT	47	7.14	2.39	7.10	43	0.02	1.68	-0.20
	Vehicle	Baseline	27	7.73	1.84	7.70				
		EOT	16	7.64	1.85	7.70	16	0.14	2.32	0.90
Neutrophils-AB (X10*9/L)	Imiquimod	Baseline	53	3.17	1.55	3.08				
		EOT	47	3.42	1.56	3.20	42	0.34	1.55	0.32
	Vehicle	Baseline	27	3.35	1.30	3.24				
		EOT	16	3.89	1.69	3.37	16	0.53	1.67	0.81

Neither Study 1494 nor Study 1495 revealed any meaningful trends in mean or median WBC, neutrophils, RBC or platelets comparing baseline to end of treatment.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 20 Study 1494: Shifts Relative to Baseline (Selected Lab Parameters)

Units	Baseline / End of Treatment	L L	L N	L H	N L	N N	N H	H L	H N	H H
Lymphocytes-AB(X10*9/L)	Imiquimod	0	2	0	4	30	0	0	0	0
	Vehicle	1	1	0	2	21	0	0	0	0
Monocytes-AB (X10*9/L)	Imiquimod	0	2	0	4	30	0	0	0	0
	Vehicle	1	3	0	3	18	0	0	0	0
Neutrophils-AB(X10*9/L)	Imiquimod	1	2	0	4	29	0	0	0	0
	Vehicle	0	2	0	2	20	1	0	0	0
Platelets (X10*9/L)	Imiquimod	0	0	0	0	31	3	0	2	0
	Vehicle	0	0	0	0	24	1	0	0	0
WBC	Imiquimod	0	3	0	6	27	0	0	0	0
	Vehicle	2	3	0	1	20	0	0	0	0

Table 21 Study 1495: Shifts Relative to Baseline (Selected Lab Parameters)

Units	Baseline / End of Treatment	L L	L N	L H	N L	N N	N H	H L	H N	H H
Lymphocytes-AB(X10*9/L)	Imiquimod	0	1	0	4	37	0	0	0	0
	Vehicle	0	0	0	0	16	0	0	0	0
Monocytes-AB (X10*9/L)	Imiquimod	1	2	0	9	30	0	0	0	0
	Vehicle	0	1	0	3	12	0	0	0	0
Neutrophils-AB(X10*9/L)	Imiquimod	1	3	0	5	33	0	0	0	0
	Vehicle	0	0	0	0	16	0	0	0	0
Platelets (X10*9/L)	Imiquimod	0	0	0	0	33	0	0	0	0
	Vehicle	0	0	0	0	12	0	0	0	0
WBC	Imiquimod	4	3	0	4	31	1	0	0	0

Vehicle	0	3	0	2	11	0	0	0	0

Integrating these data, there is a higher rate of new below normal WBC counts in the Aldara group compared with vehicle. In the Aldara group 13% (10/79) had a decrease from normal to low WBC count compared to 7% in vehicle (3/42). For absolute neutrophil counts, 11.5% of Aldara patients (9/78) and 5% of Vehicle-treated patients (2/41) had decrease from normal to low. Of note, 3 Aldara treated patients also had changes from low to normal in study 1495. None of the laboratory changes were deemed clinically significant.

Reviewer's comment: This reviewer reviewed the WBC that were below reference range in each of the two phase 3 studies. In study 1494, the lowest total WBC count at end-of-treatment was in a 6 year-old girl and was 3.6 (ref 5-14.5). In Study 1495, the lowest WBC at end-of-treatment was 3.3 from baseline of 5.4(reference range: 6-17) in a 6 year old boy (17-0475). Of note some subjects in the vehicle group also had WBC values were also below the reference range. The lowest count was taken at baseline in a 9 year-old-girl assigned to Aldara-treatment and was 2.8; this patient's WBC value was 3.3 at the end-of-treatment visit. In all, these data do not suggest clinically meaningful changes in WBC values occurred with Aldara treatment in the phase 3 clinical studies.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no drop-outs for laboratory abnormalities in the clinical studies and none of the laboratory abnormalities were considered adverse events according to the clinical investigator.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (blood pressure, pulse rate, respiratory rate, and temperature) in both phase 3 studies were collected at baseline and at each study visit (weeks 0, 2, 4, 8, 12, 16, 18, and 28). Height and weight were collected only at baseline and at week 28.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Drug-control comparisons were made for each of the two phase 3 trials.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

For study 1495: There were no statistically significant differences in changes from baseline between the imiquimod and vehicle groups for any of the vitals signs at any postbaseline visit with the exception of mean systolic blood pressure. However, this difference was small and was not driven by clinically significant abnormalities in either treatment group. The median change in systolic blood pressure from baseline to week 8 was 0 mm Hg (mean = 0.7 mm Hg) in the

imiquimod group compared to a median change of 0 mm Hg (mean = -2.5 mm Hg) in the vehicle group (p=0.019).

Reviewer's comment: This difference was small and was not driven by clinically significant abnormalities in either treatment group.

For study 1494: There were no statistically significant differences in changes from baseline between the imiquimod and vehicle groups for any of the vitals signs at any postbaseline visit.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

No dropouts for vital sign abnormalities took place in either phase 3 study.

7.1.9 Electrocardiograms (ECGs)

No ECG testing was done in the clinical trials submitted in this efficacy supplement and ECG testing was not necessary.

7.1.10 Immunogenicity

Immunogenicity was not assessed as part of the clinical studies in MC and was not needed based on the class of drug.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not assessed as part of the clinical development program in MC and was not needed.

7.1.12 Special Safety Studies

Special safety studies submitted as part of this labeling supplement included a phototoxicity study in healthy Caucasian volunteers as well as PK studies in pediatric patients ages 2-12 with molluscum contagiosum.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No instances of abuse have been reported in any of the studies in this development program and Aldara cream for topical use does not have any known potential for abuse.

7.1.14 Human Reproduction and Pregnancy Data

The studies performed were in children ages 2-12. No studies in pregnant women were performed as part of the pediatric indication in MC. Aldara is classified as pregnancy class C.

7.1.15 Assessment of Effect on Growth

Assessment of effect on growth was not done as part of the clinical studies for MC.

7.1.16 Overdose Experience

No overdose experience occurred during the clinical studies in MC.

7.1.17 Postmarketing Experience

The Dr. Nagla Wahab of Office of Surveillance and Epidemiology conducted a review summarizing all AERS post-marketing cases of erythema multiforme (EM), Stevens Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) reported with Aldara. Erythema multiforme is an acute, self-limited, and sometimes recurring skin condition, considered to be a hypersensitivity reaction associated with certain infections (herpes simplex virus, mycoplasma pneumoniae & fungal infections), medications and vaccines. Dr. Wahab's search of the AERS database (last done March 2, 2007) revealed nine unduplicated cases of EM; five cases from the United States and four foreign cases. There were six males and three females and the ages ranged from 26-82 years with a median age of 50.5 years. The onset ranged between eight days and eight weeks; median is 2 weeks (n=8). Four of the nine cases involved hospitalization. At least seven of the nine cases provided adequate information to support the association of EM with Aldara.

A case supporting an association between imiquimod and EM occurred in a 38 year old male who developed a rash within 4 to 8 weeks of treatment initiation that affected 15% BSA, had target lesions, and oral mucosal involvement. The patient had a biopsy which "confirmed" erythema multiforme. The patient was not taking any other medications at the time.

Another case, coded with hospitalization, reported a positive dechallenge response; the patient had a negative mycoplasma antibody test and a negative culture for HSV. This patient was also not taking any other concomitant medications.

Two cases of SJS and one case of TEN was reported. These cases did not have information supporting the diagnosis or the role of Aldara. Dr. Wahab's review recommended adding EM to the post-marketing adverse events section of the label. The review did not recommend adding SJS or TEN to the product label.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

A total of 470 pediatric subjects with MC were exposed to Aldara in the combined phase 3 clinical studies. Another 323 pediatric subjects were treated with Vehicle cream. The treatment period for the two phase 3 studies was 16 weeks and application of study drug to MC affected areas was 3 times weekly.

In the phase 2 study, another 62 and 63 pediatric subjects with MC received treatment with Aldara and vehicle, respectively. The treatment period for the phase 2 clinical study was a total of 8 weeks, but with a more frequent dosing regimen of 7 days per week.

7.2.1.2 Demographics

The demographic characteristics of subjects in the phase 3 clinical studies are shown in the appended study reports. The majority of the subjects were Caucasian. This is consistent with the racial composition of patients with MC reported in the literature.

7.2.1.3 Extent of exposure (dose/duration)

The frequency, amount, and duration of study drug application allowed according to the protocol is shown by study in the following table. The investigator determined the appropriate amount of study cream to administer per dose, based on each subject's weight and extent of disease.

Subjects who weighed ≤25 kg applied 1 or 2 packets of study cream, while subjects who weighed >25 kg applied 1 to 3 packets.

Table 22 Dosing Schedule by Study

Study	Phase	Frequency	Duration	Amount (Packets)
1494, 1495	3	3 times/week	16 weeks	≤25 kg → 1- 2; >25 kg → 1- 3
1490	2	7 times /week	8 weeks	≤25 kg → 1- 2; >25 kg → 1- 3
1498	1 (PK)	3 times/week	4 weeks	≤25 kg → 1- 2; >25 kg → 1- 3 Treatment areas involved ≥ 10% BSA

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No secondary clinical data sources were used to evaluate safety.

7.2.2.2 Postmarketing experience

The following cases from spontaneous reporting are unlabeled and were reported in the sponsor's safety update. Please see also review by Dr. Nagla Wahab of the Office of Surveillance and Epidemiology (OSE).

Idiopathic Thrombocytopenic Purpura:
Report from consumer. The mother of this 2-year-old male patient reports that her son started treatment with Aldara for the treatment of MC on his face five times per week. She applied the cream at night and washed it off in the morning. After 10 days, the patient began to develop bruising/petechia on his face and elbows, which continued to spread over his whole body. On Day 12, he developed a bloody nose and was taken to the emergency room where a diagnosis of immune thrombocytopenic purpura (ITP) was made. The patient was hospitalized and received IV immunoglobulin. Treatment at home continued with prednisolone sodium phosphate oral solution and patient's status was "recovering". No medical history or concomitant medications were reported. No further follow-up was reported.

Henoch-Schonlein Purpura Syndrome:
Dermatologist reports that this 3-year-old male patient started Aldara on March 20, 2000 for MC on the arms and chest. After one week of therapy (one packet per dose, three times per week every other day), he experienced local skin irritation at application site and a hypersensitivity reaction at distant sites (legs & buttocks). The child was seen by a physician on April 3, 2000. The physician diagnosed the child with Henoch-Schonlein Purpura Syndrome and lab tests were performed. Claritin (loratadine) and hydrocortisone cream were prescribed for local skin

irritation. Aldara was last used on April 1, 2000 and the child was recovering. The laboratory abnormalities had resolved by the beginning of May 2000.

Reviewer's comment: Henoch-Schonlein Purpura syndrome is an IgA-mediated small-vessel vasculitis thought to be in response to unknown foreign or endogenous antigens and is the most common form of vasculitis in childhood. In the absence of alternative etiology (e.g., infection) and given the close temporal relationship to the onset of treatment with Aldara, it is possible that Aldara is associated with Henoch-Schonlein Purpura syndrome in this patient.

Pyrexia, Convulsion:
Report from physician to sales representative. This 3-year-old child, gender unspecified, was diagnosed with MC and started using Aldara (imiquimod) Cream, 5%. The start date is assumed to be in 2005. The child used an unspecified quantity of cream with daily application. It is unknown if the cream was washed from the skin. At some time during Aldara therapy, the child developed a fever (temperature unspecified) and a seizure. The child was admitted to the hospital. Aldara therapy was stopped (date unspecified) and the events resolved. No medical history or concomitant medications were reported.

Reviewer's comment: It seems unlikely that Aldara was the primary cause of febrile convulsion in this child. An infectious cause is more likely. It is possible, however, that Aldara could have exacerbated the fever leading to febrile convulsions in this patient.

Diarrhea, Vomiting, Liver Function Tests Elevation, Dehydration:
A medical assistant for a dermatologist reported that a 6-year-old girl with MC lesions on her upper thighs, lower back and groin area began using Aldara cream, one packet three times weekly, on May 26, 2004. The mother was told to only apply one packet to all the lesions once weekly, but the mother used one full packet three times weekly. On about (b) (6) the patient experienced vomiting and diarrhea. The patient was seen in the emergency room within the following two days, and it was found that the patient had elevated liver function tests and was dehydrated. It was recommended that Aldara therapy be discontinued. The last dose of Aldara was on about (b) (6) The vomiting had resolved (date unspecified) and the diarrhea was continuing at the time of this report. Concomitant medications Elidel (pimecrolimus topical) and Dermatop (prednicarbate) were reported for a history of eczema.

Reviewer's comment: The dose described in this report is similar to what was studied in the phase 3 studies for MC. The illness reported seems more likely related to an alternative etiology (e.g., viral gastroenteritis) than to Aldara therapy.

Abdominal Pain, Myalgia, Local Swelling, Application Site Erythema:
A nurse reported that a 53 year old male with a diagnosis of MC on his abdomen and waist line was prescribed Aldara cream. He was instructed to dose three times per week, but the patient misunderstood the instruction and was dosing three times per day. He used a total of one packet a day and left the cream on continuously for 24 hours. Twelve days into therapy, he began to experience abdominal cramp, muscle pain and swelling in the groin area and reported redness at the application site. He was advised by the clinic not to resume therapy. The adverse events

were ongoing at the time of report. No medical history or concomitant medications were reported.

Reviewer's comment: This case is associated with misuse of the product and likely does not represent a new safety signal.

7.2.2.3 Literature

No literature was submitted as part of this labeling supplement.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience was adequate especially given that none of the clinical studies succeeded in demonstrating clinical efficacy for MC in pediatric patients.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new animal or in-vitro data was submitted as part of this labeling supplement and none was deemed necessary.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing included vital signs, evaluation of signs and symptoms of molluscum contagiosum and hematology in a subset of subjects in the phase 3 clinical studies. The testing appeared adequate with the exception that the subjects with treatment emergent laboratory abnormalities in WBC and neutrophil counts were not retested to document the final outcome.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

A drug-drug interaction studies were not conducted as part of this application, and none are needed. The PK evaluation was done in Study 1498 and was reviewed by Dr. Ghosh. This was deemed adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

No further study is recommended for the indication of molluscum contagiosum.

7.2.8 Assessment of Quality and Completeness of Data

The initial data provided for safety review was incomplete in that no data sets were present in the original application, no integrated review of safety was submitted and the results of the phase 2 clinical study were not provided as part of this labeling supplement. Since then, the clinical reviewer requested and has received clinical datasets and has requested report of the phase 2 clinical study to be submitted to the NDA as well as ISS (with the safety update).

7.2.9 Additional Submissions, Including Safety Update

The sponsor submitted a safety update on February 15, 2007. The results of this update have been integrated into this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

In the combined phase 3 studies, the most frequently reported possibly or probably related AE was application site reaction; 31% (144/470) of Aldara-treated subjects and 20% (47/232) of vehicle-treated subjects reported at least one application site reaction. Actively assessed, local skin reactions such as erythema, edema, erosion, weeping/exudate, flaking/scaling and scabbing/crusting were noted in a higher proportion of patients in the active treatment group compared with vehicle (see section 7.1.5.5). These findings are consistent with the known safety profile of the Aldara.

Findings from spontaneous reports included cases of erythema multiforme cases which were identified from the AERS database by Dr. Nagla Wahab. Also identified from the sponsor's Safety Update report, there was one report of Henoch-Schonlein purpura syndrome, a case of ideopathic thrombocytopenic purpura and a case of febrile convulsion. Although, these events are not from a controlled database and it is very difficult to establish causality, the potential health impact of these events warrants inclusion in the post-marketing section of the label.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The reviewer pooled safety data from the two phase 3 clinical trials and also evaluated the safety data separately.

7.4.1.2 Combining data

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Explorations for dose dependency for adverse findings were limited to the findings of treatment emergent below normal WBC counts and neutrophil counts. There was not a clear relationship between the body surface area treated and the finding of below normal WBC count.

7.4.2.2 Explorations for time dependency for adverse findings

The treatment duration was 16 weeks. No explorations for time-dependency of adverse reactions were performed.

7.4.2.3 Explorations for drug-demographic interactions

Safety in the pooled dataset were evaluated for subjects under age 4 and for those age 4 and above.

7.4.2.4 Explorations for drug-disease interactions

No specific explorations for drug-disease interactions were performed.

7.4.2.5 Explorations for drug-drug interactions

No explorations for drug-drug interactions were performed.

7.4.3 Causality Determination

As discussed in the safety review, local skin reactions such as erythema, edema, erosion, weeping/exudate, flaking/scaling and scabbing/crusting were noted in a higher proportion of patients in the active treatment group compared with vehicle. These finding are in keeping with the known profile of Aldara cream from studies in adults in other indications.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen studied was similar to that used for condylomata acuminata: topical administration three times weekly for up to 16 weeks or until the investigator confirmed that the lesions had cleared. The maximum amount of study drug that could be used was dependent on body weight with subjects weighing less than 25 kg applying up to 2 sachets and those weighing 25 kg or more applying up to 3 sachets per application. The subject's legal parental custodian(s) were to apply the study cream to all MC lesions in the application area(s) and any new lesions that have appeared before the end-of-treatment visit.

8.2 Drug-Drug Interactions

No drug-drug interaction studies were performed as part of this labeling supplement.

8.3 Special Populations

This submission focuses on the use of Aldara for MC in children aged 2-12 years.

8.4 Pediatrics

Aldara has had considerable off-label use in the indication MC in pediatric patients. The studies in this submission are were conducted under the Agency's Written Request for pediatric studies and evaluated Aldara for MC in subjects aged 2-12 years. These studies failed to demonstrate efficacy.

8.5 Advisory Committee Meeting

No Advisory Committee Meeting was held for this labeling supplement.

8.6 Literature Review

No literature review was conducted as part of this NDA supplement review.

8.7 Postmarketing Risk Management Plan

No other postmarketing risk management plan is necessary as part of this labeling supplement.

8.8 Other Relevant Materials

No materials were reviewed other than those submitted under this labeling supplement and the consultative review by Dr. Wahab in OSE.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor has submitted a labeling supplement for the use of Aldara for MC in children aged 2-12 years conducted under pediatric written request. Two phase 3 randomized, controlled studies failed to demonstrate efficacy in MC as measured by complete clearance after 16 weeks of 3 times weekly application. Aldara was also studied in a subgroup of children with periocular MC and was not shown to be effective. In general, the local safety appeared to be consistent with what is known from the study in other indications. This supplement will result in an update the pediatric section of the label to include these findings.

9.2 Recommendation on Regulatory Action

The sponsor is not pursuing efficacy claims regarding MC, and this reviewer recommends revision to package insert to reflect that the treatment of MC is a limitation of use based on the negative results of these studies.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No other postmarketing risk management plan is necessary as part of this labeling supplement.

9.3.2 Required Phase 4 Commitments

No required phase 4 commitments are necessary as part of this labeling supplement.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are necessary as part of this labeling supplement.

9.4 Labeling Review

Please see the appended line-by-line labeling review for details.

9.5 Comments to Applicant

There are no comments to applicant at this time.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1. 1490_IMIQ

Study Title: 1490-IMIQ Double-Blind, Vehicle-Controlled Study of Imiquimod Cream, 5% in Pediatric Subjects with Molluscum Contagiosum to Evaluate Safety and Efficacy of Daily Dosing During 8 Weeks of Treatment

Phase of Development: 2

Study Period: 18 November 2003- 18 January 2005

Study Centers: 9 study centers (7 in United States and 2 in Canada)

Primary Objective: to evaluate the efficacy of imiquimod cream, 5% (imiquimod) on molluscum contagiosum (MC) lesions in pediatric subjects when applied daily for 8 weeks of treatment.

Methods: This study included multiple applications of imiquimod versus vs. vehicle cream applied topically 7 times per week (7x/wk) for up to 8 weeks to MC lesions in pediatric subjects aged 2 to 12 years with a minimum of 5 MC lesions. For eligible subjects, 5 to 30 MC lesions were selected for treatment with study cream and enrolled subjects were randomized in a 1:1 ratio to the imiquimod or vehicle treatment group. Subjects/legal parental custodian(s) and investigators were unaware of the study cream assignment. Subjects' legal guardian(s) applied study cream once daily for 8 weeks or until the study visit where the investigator determined all MC lesions in the treatment area(s) had cleared.

Study assessments: clinic visits at weeks 2, 4, 8, and 12 for efficacy and safety
Evaluation of the subject's MC lesions included baseline MC lesion assessment, lesion count, documentation of lesion location, and photographs of the treatment area(s). At each study visit the investigator recorded whether each MC lesion treated with study cream had cleared. Subjects who were clear of all MC lesions in the treatment area(s) at weeks 2, 4, or 8 completed the EOS procedures instead of the scheduled treatment period visit procedures. This study did not include laboratory evaluations.

Protocol Amendments: Modifications were made to the original protocol with Amendments 1 and 2, dated 14 August 2003 and 22 March 2004, respectively. The second issue of the protocol incorporated a modified local skin reaction intensity scale, for which the intensity was determined through qualitative assessments. The modified scale also included the additional local skin reactions of weeping/exudate. The methods described in this report reflect the changes made as a result of Amendments 1 and 2.

Number of Subjects: Randomization was 1:1 (active:vehic1e) for a planned number of 120 subjects. Of the 134 subjects screened, a total of 125 subjects were enrolled.

Main Eligibility Criteria:
- 2 to 12 years of age, inclusive;
- presented with 5 investigator-confirmed MC lesions;
- free of significant skin conditions and tattoos in the treatment area(s); and
- willing to comply with all study requirements including evaluations and procedures.

MC lesions on the eyelid margin, and inguinal region and buttocks (if the subject wore diapers), were excluded from treatment and were not counted as part of the entry criteria.

Criteria for Evaluation:
Efficacy: Efficacy was monitored at each study visit by determining whether each individual MC lesion selected for treatment with study cream had cleared.
Safety: At each study visit, safety was measured through AE monitoring, local skin reactions assessments, vital signs measurements, and use of concomitant medications. Physical examinations were performed at the pre-study and end-of-treatment visit.
Skin Quality assessments were performed at the end-of-study visit only.

Statistical Methods: The primary data set analyzed for efficacy and safety was the intent-to-treat (ITT) data set, consisting of all randomized subjects. Treatment groups were compared with respect to the primary variable (End-of-study visit complete clearance of baseline MC lesions) by means of a Cochran-Mantel-Haenszel (CMH) Test, which adjusts for multiple study centers. Statistical tests were two-sided and conducted at the alpha = 0.05 level.

Results:
Demographics: (N=125)
Sex: Females n = 54 Males n = 71

Age: Mean = 5.5 yrs Range 1 to 12
Race: White n = 113 (90.4%) Black n = 5 (4.0%) Asian/Pacific Islander n = 6 (4.8%)
Unknown n = 1 (0.8%)

Efficacy:
For the ITT data set, imiquimod subjects had a complete clearance rate of baseline MC lesions of 24% (15/62) vs. of 21% (13/63) for vehicle subjects (p=0.6840). There were no statistically significant differences between the imiquimod and vehicle treatment groups with respect to the complete clearance rate of all MC lesions (p=0.5085) or the partial clearance rate of baseline MC lesions (p=0.9320). The distribution in time to complete clearance was not significantly different (p = 0.8052) between the imiquimod and vehicle treatment groups. For the imiquimod and vehicle groups, the Cochran-Armitage test for trend did not identify a statistically significant association between local skin reaction intensity and complete clearance of baseline MC lesions in any of the 6 local skin reaction categories.

Safety:
Four subjects (3 imiquimod, 1 vehicle) discontinued because of an AE; the 3 imiquimod subjects discontinued due to an application site reaction. The most frequently reported AE considered by the investigator to be possibly or probably related to study drug was application site reactions, with 51.6% (32/62) of imiquimod subjects and 34.9% (22/63) of vehicle subjects affected.

A statistically significant difference between the imiquimod and vehicle groups was recorded for the application site reaction included term of scabbing at target site (p=0.017). Of the local skin reactions assessed and recorded by the investigator, there were statistically significant treatment differences in the distribution of maximum severity scores between imiquimod and vehicle groups for erythema, edema, erosion/ulceration, weeping/exudate, and scabbing/crusting. The most frequently recorded LSR was erythema. Findings from the physical examination and vital signs measurements were consistent with the age of the subject population. For the skin quality assessment, there were statistically significant differences between the imiquimod and vehicle groups in the severe hyperpigmentation scores.

Two imiquimod subjects experienced "other significant AEs". One subject experienced exanthem (outcome listed as persistent) and one subject experienced a superinfection (outcome listed as recovered). No severe AEs, deaths, or pregnancies were reported during the study.

Table 23 Discontinuations From the Study Due to Adverse Events

Study Center No./ Subject No.	Study Cream	Primary Reason for Discontinuation	Intensity/ Relationship to Study Drug	Action Taken/ Outcome	Comments
0002/0041	Imiquimod	AE/application site reaction	Moderate/ Possibly	Stopped study cream/ persistent	Exanthem. Active atopic dermatitis and allergies.
0006/0033	Imiquimod	AE/application site reaction	Moderate/ Probably	Stopped study cream/ persistent	Pain
0008/0107	Imiquimod	AE/application site reaction	Moderate/ Probably	Stopped study cream/ required therapy/	Superinfection.
0008/0106	Vehicle	AE	Mild/ Possibly	Stopped study cream/ persistent	Perceived hypopigmentation

Some patients were found to have complications due to treatment including infections of the treatment area. In one case, a patient was prescribed cephalexin and developed an allergic drug reaction.

Conclusions: Imiquimod 5% cream, dosed once daily for up to 8 weeks, did not show a statistically significant difference in complete clearance of baseline MC lesions from vehicle cream.

Four subjects (3 imiquimod, 1 vehicle) discontinued because of an AE; the 3 imiquimod subjects discontinued due to an application site reaction. Imiquimod use was associated with a higher rate of skin reactions and hyperpigmentation.

10.1.2. 1494_IMIQ

Phase of Development: 3

Study Title: Phase III Vehicle-controlled, Double-blind Study to Assess the Safety and Efficacy of Imiquimod Cream, 5% for the Treatment of Molluscum Contagiosum in Pediatric Subjects

First Subject Enrolled: 18 February 2004 Last Subject Completed: 18 May 2005

Study Centers: 19 study centers in the USA

The primary objective was to evaluate the efficacy of imiquimod cream 5% applied 3 times per week for the treatment of molluscum contagiosum (MC) lesions in pediatric subjects.

Diagnosis and Main Criteria for Inclusion: Eligible subjects:
- Had ≥2 clinically verified MC lesions (at least half had ≥5 lesions) not located on buttocks, or inguinal region or on hands only
- Were 2 to 12 years old

Number of Subjects: 300 subjects were planned; 323 subjects were actually enrolled.

Efficacy Endpoints:
The primary efficacy parameter was complete clearance of all MC lesions (complete clinical resolution) from treatment initiation to the week 18/efficacy visit.

Secondary efficacy parameters included partial clearance, defined as ≥50% reduction from the baseline lesion count, and the and the change in total lesion count. Time to complete clearance was also compared between treatment groups.

Methods: This was a randomized, vehicle-controlled, double-blind, parallel group, phase III, multicenter study conducted in children aged 2 to 12 years of age who had ≥2 clinically verified MC lesions. Enrollment was monitored to ensure at least 50% of subjects had at least 5 MC lesions, at least 50% of subjects were under 6 years of age, and a sufficient number of subjects enrolled with periocular lesions. Subjects were randomized 2:1 (imiquimod:vehicle) and applied study cream 3x/wk for up to 16 weeks (or until complete resolution of all MC lesions) to all

target MC lesions. Subjects who weighed <25 kg applied up to 2 sachets of study cream, while subjects who weighed ≥25 kg applied up to 3 sachets. At the screening/treatment initiation visit, MC lesions and application area locations were recorded on a provided body diagram. Subjects reported to the clinic at treatment weeks 2, 4, 8, 12, and 16, and posttreatment at week 18 for efficacy assessments, and week 28 for end-of-study procedures. At each study visit, MC lesions were counted and recorded, and safety procedures were performed. Also, the subject's diary was reviewed for compliance. Subjects returned at week 18 for the primary efficacy and post-treatment safety assessments. All subjects who did not clear their MC lesions as well as subjects who did not complete the 16 weeks of treatment were to report to the clinic at week 28 for final safety and efficacy assessments.

Table 24 Local Skin Reactions were Graded as Follows

Local Skin Reactions	Intensity Definitions			
	None	Mild	Moderate	Severe
Erythema	None	Faint to mild redness in the application area	Moderate redness in the application area	Intense redness in the application area
Edema	None	Mild visible or barely palpable swelling / induration of the application area	Easily palpable swelling / induration of the application area	Gross swelling / induration of the application area
Erosion / Ulceration	None	Superficial skin denudation at the application area	Erosion at the application area	Ulceration at the application area
Weeping / Exudate	None	Minimal exudates at the application area	Moderate exudates at the application area	Heavy exudates at the application area
Flaking / Scaling / Dryness	None	Mild dryness / flaking in the application area	Moderate dryness / flaking in the application area	Severe dryness / flaking in the application area
Scabbing / Crusting	None	Crusting at the application area	Serous scab at the application area	Eschar in the application area

The investigator performed skin quality assessments of each application area at the end-of-treatment visit and week 18 and 28 visits. The intensity of each characteristic was graded by the investigator (none, mild, moderate, or severe).

Characteristics assessed included:
• Hyperpigmentation (independent of texture change or hypopigmentation);
• Hypopigmentation (independent of texture change or hyperpigmentation);
• Degree of scarring (texture change independent of pigmentary changes); and
• Atrophy.

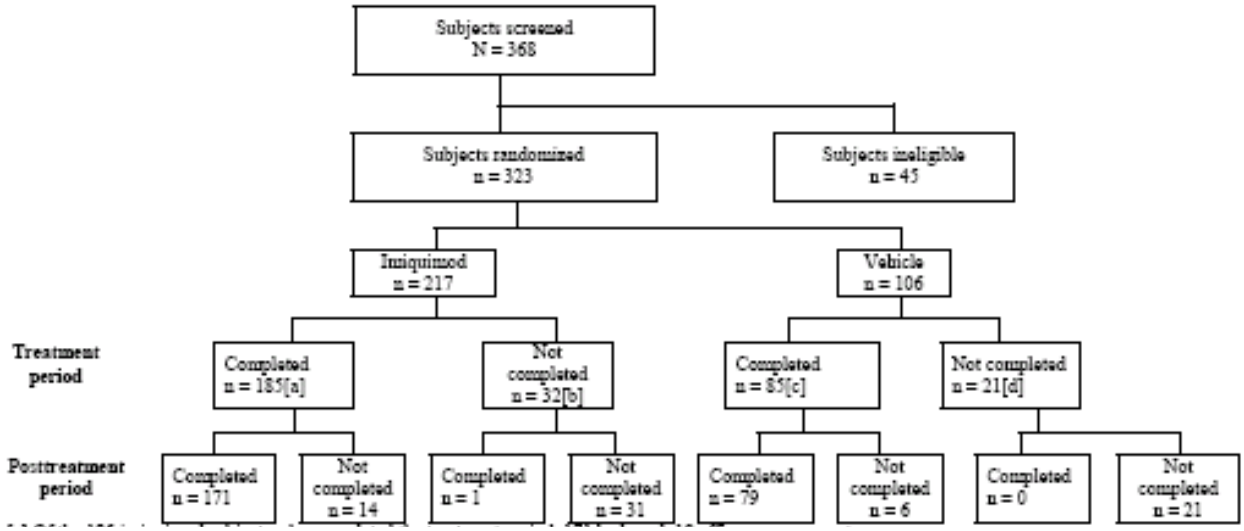
The investigator also counted and recorded the number of pits in each application area at the week 18 and 28 visits. A pit was defined as a hollow depression on the skin left by a MC lesion.

Duration of Treatment: MC lesions were treated 3x/wk for up to 16 weeks, or until the investigator determined that all MC lesions had cleared.

Statistical Methods:
The primary dataset analyzed for efficacy and safety was the intent-to-treat (ITT) dataset, consisting of all randomized subjects.

Treatment groups were compared with respect to the primary variable (complete clearance rate at the week 18 study visit) by means of the Cochran-Mantel-Haenzsel (CMH) Test, which adjusts for multiple study centers.

Disposition:
Subject disposition throughout the entire study is summarized below. All randomized subjects were expected to complete posttreatment visits even if they did not complete the treatment period.



Overall, 368 subjects were screened and 323 were randomized to study cream. A total of 217 subjects were randomized to imiquimod cream, and of these 185 subjects completed the treatment period and 171 completed both the treatment period as well as the post-treatment period. A total of 106 subjects were randomized to vehicle cream and of these 85 subjects completed the treatment period and 79 completed both the treatment period as well as the post-treatment period.

Table 25 Number (%) of Subjects Discontinued During the Treatment Period by Primary Reason

Primary Reason for Discontinuation	Imiquimod (n=217)	Vehicle (n=106)
Adverse Event	2 (1%)	1 (1%)
Lost to Follow-up	23 (11%)	12 (11%)
Personal	5 (2%)	5 (5%)
Lack of Therapeutic Effect	1 (<1%)	2 (2%)
Other	1 (<1%)	1 (1%)
Total	32 (15%)	21 (20%)

Overall, 15% (32/217) and 20% (21/106) of imiquimod and vehicle subjects, respectively, discontinued from the 16-week treatment period. The most common reason for discontinuation in each treatment group was "lost to follow-up".

A summary of protocol deviations is shown in the following table.

Table 26 Protocol Deviations

Departure Code	Imiquimod	Vehicle
Total departures	35	23
Violation inclusion/exclusion criteria	4	1
Study treatment dosing error	15	12
Use of excluded treatments	8	3
Noncompliance with procedures	8	7

A total of 35 subjects had protocol violations in the active group compared with 23 in the vehicle group. The most common type of protocol deviation in each group was dosing error.

Reviewer's comment: The proportions of subjects for whom protocol violations were reported would not likely have had an impact on the overall study results.

Baseline Demographics

Table 27 Baseline Demographics

Variable Description		Imiquimod (n=217)	Vehicle (n=106)	Total (n=323)
Gender	Female	109 (50%)	51 (48%)	160 (50%)
	Male	108 (50%)	55 (52%)	163 (50%)
Age at Screening	Median	5	4	5
	Minimum	2	2	2
	Maximum	12	12	12
Height (cm)	Median	112.5	111.3	111.8
	Minimum	81	87	81
	Maximum	165	165	165
Weight (kg)	Median	20.1	20.2	20.1
	Minimum	12	11	11
	Maximum	73	64	73
Race	White	203 (94%)	102 (96%)	305 (94%)
	Black/African American	11 (5%)	4 (4%)	15 (5%)
	Asian	1 (<1%)	0 (0%)	1 (<1%)
	Native Hawaiian/ Other Pacific Islander	2 (1%)	0 (0%)	2 (<1%)
Ethnicity	Unknown	1 (<1%)	0 (0%)	1 (<1%)
	Not Hispanic / Latino	187 (86%)	93 (88%)	280 (87%)
	Hispanic / Latino	29 (13%)	13 (12%)	42 (13%)
Periocular Lesions	Yes	14 (6%)	12 (11%)	26 (8%)
	No	203 (94%)	94 (89%)	297 (92%)

Overall, the median age was 5. Most subjects were Caucasian (94%) and most were not Hispanic or Latino (87%). The demographic characteristics were similar across the two treatment groups. Periocular lesions were present in a higher number in the vehicle arm (11% in vehicle and 6% in active).

The following table shows the age distribution for subjects.

Table 28 Age Distribution

Age Group (years)	Imiquimod (n=217)	Vehicle (n=106)
2 - 3	62 (29%)	31 (29%)
4 - 5	60 (28%)	35 (33%)
6 - 7	55 (25%)	21 (20%)
8 - 9	30 (14%)	12 (11%)
10 - 12	10 (5%)	7 (7%)

In the imiquimod group, 29% of subjects in each of the two treatment groups were < 4 years old. In the imiquimod group, 56% (122/217) of subjects were < 6 years old compared to 62% (66/106) of subjects in the vehicle group. Allergic rhinitis was present in approximately 19% of the study population.

A history of atopic dermatitis was present in 17% of imiquimod-treated subjects compared with 12% of vehicle-treated subjects.

Drugs taken within 4 weeks of treatment initiation or after the treatment initiation visit were considered concomitant medications. Topical steroids were used by 10% (32/323) of the subjects, with more imiquimod subjects (12%, 27/217) reporting use than vehicle subjects (5%, 5/106).

Table 29 Number of Baseline MC Lesions

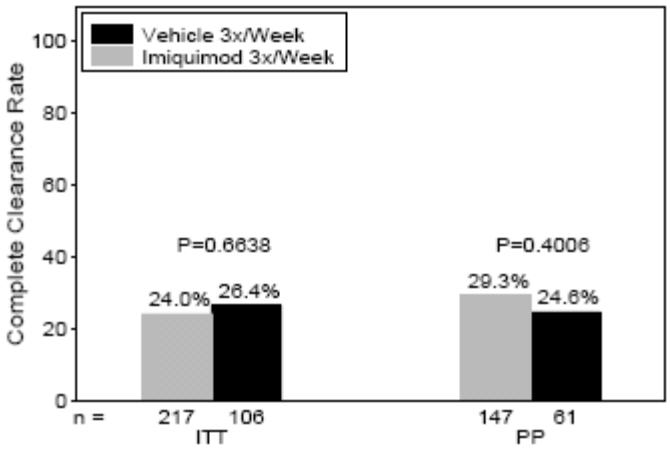
No. of Baseline MC Lesions	Imiquimod (n=217)	Vehicle (n=106)	Total (n=323)
< 5	13 (6%)	9 (8%)	22 (7%)
5 - 15	76 (35%)	41 (39%)	117 (36%)
16 - 30	66 (30%)	29 (27%)	95 (29%)
31 - 50	29 (13%)	15 (14%)	44 (14%)
> 50	33 (15%)	12 (11%)	45 (14%)
Mean	30	24	28
Median	18	16	17
SD	45	24	40
Minimum	2	2	2
Maximum	462	160	462
25th Percentile	11	10	10
75th Percentile	33	32	33

The distribution of baseline MC counts was skewed to the right. The median number of MC lesions at baseline was numerically higher in the active treatment group compared with vehicle, 18 and 16, respectively.

Primary Efficacy Analysis:

For the ITT dataset, 24% (52/217) of imiquimod subjects and 26% (28/106) of vehicle subjects achieved complete clearance at the week 18/efficacy assessment visit (p=0.6638). Subjects who did not have a week 18 MC lesion assessment (45 subjects in the imiquimod group and 22 subjects in the vehicle group) were considered "not completely clear" in the ITT analysis of complete clearance. The following figure shows the rates of complete clearance by ITT study population as well as per protocol (PP) population. The differences between treatment groups were not statistically significant.

Figure 1 Complete Clearance Rates at Week 18



Subgroup Analyses:

Table 30 Subgroup Analyses

Subgroup		Imiquimod	Vehicle
Sex	Female	22% (24/109)	29% (15/51)
	Male	26% (28/108)	24% (13/55)
Race	White	24% (48/203)	26% (27/102)
	Nonwhite	29% (4/14)	25% (1/4)
Ethnicity	Unknown	0% (0/1)	--% (0/0)
	Hispanic/Latino	24% (7/29)	23% (3/13)
	Not Hispanic/Latino	24% (45/187)	27% (25/93)
Age Group (years)	<4	19% (12/62)	13% (4/31)
	4 - 5	20% (12/60)	29% (10/35)
	6 - 7	26% (14/55)	38% (8/21)
	8 - 9	33% (10/30)	33% (4/12)
	>9	40% (4/10)	29% (2/7)
Periocular Lesions	Yes	29% (4/14)	33% (4/12)
	No	24% (48/203)	26% (24/94)
Atopic Dermatitis	Yes	27% (10/37)	8% (1/13)
	No	23% (42/180)	29% (27/93)
Dosing Compliance	Unknown	0% (0/11)	0% (0/5)
	≥100%	18% (11/63)	29% (9/31)
	90 - <100%	31% (21/68)	19% (6/31)
	80 - <90%	28% (9/32)	46% (6/13)
	70 - <80%	36% (5/14)	38% (3/8)
	60 - <70%	50% (4/8)	67% (2/3)
	<60%	10% (2/21)	13% (2/15)
Baseline Erythema	Any	26% (30/114)	31% (16/52)
	None	21% (22/103)	22% (12/54)
MC Duration (months)	Unknown	25% (1/4)	0% (0/4)
	0 - <3	30% (16/54)	26% (5/19)
	3 - <6	17% (9/53)	27% (7/26)
	6 - <12	31% (19/62)	24% (8/34)
	≥12	16% (7/44)	35% (8/23)

No meaningful trends were noted in response rates by MC duration, dosing compliance, periocular location, age, race, ethnicity, or gender. A numerically higher proportion of subjects with atopic dermatitis responded in active (27% or 10/37) compared with vehicle (8% or 1/13). Similar trends were not observed in Study 1495, however.

Table 31 Week 18 Complete Clearance Rate by Number of Baseline Lesions

Baseline MC Lesion Count	Imiquimod	Vehicle
≤15 MC Lesions	22% (20/89)	18% (9/50)
>15 MC Lesions	25% (32/128)	34% (19/56)

Table 32 Week 18 Complete Clearance Rate by Number of Baseline Lesion Deciles

Decile of Baseline MC Count	Baseline MC Count	Imiquimod N= 217		Vehicle N= 106	
1	2 - <6	37	7/19	38	5/13
2	6 - <8	33	5/15	9	1/11
3	8 - <11	10	2/19	0	0/6
4	11- <14	4	1/25	21	3/14
5	14- <17	26	5/19	20	2/10
6	17 - <22	21	6/29	67	8/12
7	22- <28	37	7/19	33	3/9
8	28 - <38	31	8/26	33	3/9
9	38 - <55	10	2/21	14	2/14
10	55 - 462	36	9/25	12	1/8

There were no meaningful differences or trends in complete response by decile of baseline MC count.

Secondary Efficacy Endpoint

The following table shows the partial clearance rates. The partial clearance rate was defined as the proportion of subjects with at least a 50% reduction in the number of MC lesions counted at baseline in all 10 body sites.

Table 33 Week 18 Partial Clearance Assessment

	Imiquimod (n=217)	Aldara (n=106)
Partial Clearance	108 (50%)	48 (45%)
Not Partial Clearance	64 (30%)	36 (34%)
Incomplete Assessment	45 (21%)	22 (21%)

There was no meaningful difference between treatment groups in partial clearance.

Safety:

Extent of Exposure:

Subjects applied 3 doses per week for up to 16 weeks (48 doses), stopping prior to 16 weeks of treatment if the investigator determined the subject was completely clear of MC lesions. Subjects weighing <25 kg were to apply up to 2 packets per dose application while subjects weighing ≥25 kg could apply up to 3 packets per dose application. Each packet contains 250 mg of cream, or 12.5 mg imiquimod. For the subjects that returned their dosing diary, the median

number of doses applied was 44 (range, 1 to 64) for the imiquimod group and 45 (range, 0 to 63) for the vehicle group.

Table 34 Study Drug Compliance

Total No. of Doses Applied	Imiquimod (n=217)	Vehicle (n=106)
Unknown	11 (5%)	5 (5%)
0 - 6	5 (2%)	4 (4%)
7 - 12	12 (6%)	6 (6%)
13 - 18	8 (4%)	2 (2%)
19 - 24	13 (6%)	6 (6%)
25 - 30	6 (3%)	6 (6%)
31 - 36	17 (8%)	4 (4%)
37 - 42	24 (11%)	15 (14%)
43 - 48	92 (42%)	39 (37%)
>48	29 (13%)	19 (18%)
Median	44	45
Minimum	1	0
Maximum	64	63

Exposure to study drug was similar between the two treatment groups.

The incidence rate for application site reactions was higher in imiquimod-treated subjects compared with vehicle (imiquimod, 36% vs. vehicle, 20%; p=0.004). For the subset of subjects less than 4 years old, a higher proportion of subjects had lymphadenopathy, 11% (7/62) vs. vehicle, 0% (0/31).

For subjects with periocular lesions, the most frequently reported AE by preferred term was application site reaction, occurring in 7% (1/14) of imiquimod subjects and 25% (3/12) of vehicle subjects. Blepharitis was reported by 1 vehicle subject and 0 imiquimod subjects.

Skin quality assessments were made at EOT, week 18, and week 28 visits. The incidence of hyperpigmentation, hypopigmentation, scarring and atrophy are described by most severe intensity observed in the following table.

Table 35 Study 1494 Skin Quality Assessments

Skin Quality Variable	Intensity	Imiquimod (n=190)	Vehicle (n=90)
Hyperpigmentation	None	101 (53.2%)	54 (60.0%)
	Mild	70 (36.8%)	30 (33.3%)
	Moderate	18 (9.5%)	5 (5.6%)
	Severe	1 (0.5%)	1 (1.1%)
Hypopigmentation	None	143 (75.3%)	70 (77.8%)
	Mild	40 (21.1%)	18 (20.0%)
	Moderate	6 (3.2%)	2 (2.2%)
	Severe	1 (0.5%)	0 (0.0%)
Scarring	None	132 (69.5%)	68 (75.6%)
	Mild	47 (24.7%)	20 (22.2%)
	Moderate	11 (5.8%)	2 (2.2%)
	Severe	0 (0.0%)	0 (0.0%)
Atrophy	None	138 (72.6%)	72 (80.0%)
	Mild	47 (24.7%)	14 (15.6%)
	Moderate	5 (2.6%)	4 (4.4%)
	Severe	0 (0.0%)	0 (0.0%)

In the Aldara treatment group, there was a tendency for hyperpigmentation, hypopigmentation and scarring to have a higher incidence of moderate to severe ratings compared with vehicle. Overall, hyperpigmentation was noted in 47% (89/190) of Aldara-treated subjects in at least 1 body site during the study compared to 40% (36/90) of vehicle subjects. Approximately 10% of Aldara-treated subjects had moderate to severe hyperpigmentation compared with 7% of vehicle treated subjects. Hypopigmentation was noted in 25% (47/190) of Aldara-treated subjects compared to 22% (20/90) of vehicle subjects, and 4% of Aldara-treated patients experience moderate to severe hypopigmentation compared with 2% of vehicle-treated patients. Scarring was noted in 30% (58/190) of Aldara-treated subjects compared to 24% (22/90) of vehicle-treated subjects, and 6% of Aldara-treated subjects experienced moderate to severe scarring compared with 2% of vehicle treated subjects.

Reviewer's comment: In Study 1495, there was also a higher proportion of subjects in the active arm who experienced hyperpigmentation and scarring. The proportion of subjects who experienced hypopigmentation in Study 1495 were the same between the two treatment groups (18%, respectively). In Study 1495, the overall rates of atrophy was similar between the two treatment groups, but there was a higher proportion of subjects with moderate atrophy in the vehicle arm. (See appendix 10.1.3).

Table 36 Incidence of Severe Adverse Events (source table 14.3.1.12)

Body System Preferred Term	Imiquimod 3x/Week (n=217)	Vehicle 3x/Week (n=106)
APPLICATION SITE DISORDERS	7 (3.2%)	1 (0.9%)
APPLICATION SITE REACTION	7 (3.2%)	1 (0.9%)
BODY AS A WHOLE - GENERAL DISORDERS	1 (0.5%)	0 (0.0%)
FEVER	1 (0.5%)	0 (0.0%)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	1 (0.5%)	0 (0.0%)
ENCEPHALOPATHY	1 (0.5%)	0 (0.0%)
MUSCULO-SKELETAL SYSTEM DISORDERS	1 (0.5%)	0 (0.0%)
MYALGIA	1 (0.5%)	0 (0.0%)
RESISTANCE MECHANISM DISORDERS	1 (0.5%)	1 (0.9%)
INFECTION BACTERIAL	0 (0.0%)	1 (0.9%)
UPPER RESP TRACT INFECTION	1 (0.5%)	0 (0.0%)
RESPIRATORY SYSTEM DISORDERS	0 (0.0%)	1 (0.9%)
ASTHMA	0 (0.0%)	1 (0.9%)
SECONDARY TERMS	3 (1.4%)	0 (0.0%)
INFLICTED INJURY	3 (1.4%)	0 (0.0%)
SKIN AND APPENDAGES DISORDERS	2 (0.9%)	1 (0.9%)
FURUNCULOSIS	0 (0.0%)	1 (0.9%)
RASH	1 (0.5%)	0 (0.0%)
URTICARIA	1 (0.5%)	0 (0.0%)

Serious Adverse Events:

3x/Week Treatment	Study/Center/ Subject No.	Preferred Term (Verbatim Text)	Onset Day	Duration of AE (days)	Action Taken	Outcome
Imiquimod	1494/0012/0081	INFLICTED INJURY (BROKEN LEFT HUMERUS)	25	34	Required therapy	Recovered
	1494/0020/0105	ENCEPHALOPATHY (ANOXIC BRAIN INJURY/ENCEPHALOPATHY)	67		Required therapy/stopped	Persistent
		INFLICTED INJURY (CUTTING OF THROAT)	67	22	Required therapy/stopped	Recovered
		INFLICTED INJURY (STATUS POST PENETRATING NECK INJURY INCLUDING INJURY TO RIGHT LOBE OF THYROID GLAND AND RIGHT INTERNAL JUGULAR VEIN)	67		Required therapy/stopped	Persistent
Vehicle	1494/0005/0313	ASTHMA (ASTHMA)	81	5	Required therapy	Recovered

Conclusions: Based on the results of this study, the efficacy of imiquimod dosed 3x/wk for up to 16 weeks is similar to vehicle cream. In addition to the complete and partial clearance endpoints, there were no other efficacy variables that showed a significant difference between imiquimod and vehicle cream.

In this study, the rate of application site reactions (ASR) was 36% in the Aldara group compared with 20% in the vehicle group. There was also a higher rate of severe ASR in the Aldara group compared with vehicle (3% vs. 1%). This is in keeping with the known safety profile of Aldara.

10.1.3. 1495_IMIQ

Phase of Development: 3

Study Title: Phase III Vehicle-controlled, Double-blind Study to Assess the Safety and Efficacy of Imiquimod Cream, 5% for the Treatment of Molluscum Contagiosum in Pediatric Subjects

First Subject Enrolled: 29 January 2004 Last Subject Completed: 24 May 2005

Study Centers: 19 study centers in the USA

The study design was the same as that of Protocol 1495.

Disposition:

Subject disposition throughout the entire study is summarized below.

Figure 2 Subject Disposition Study 1495

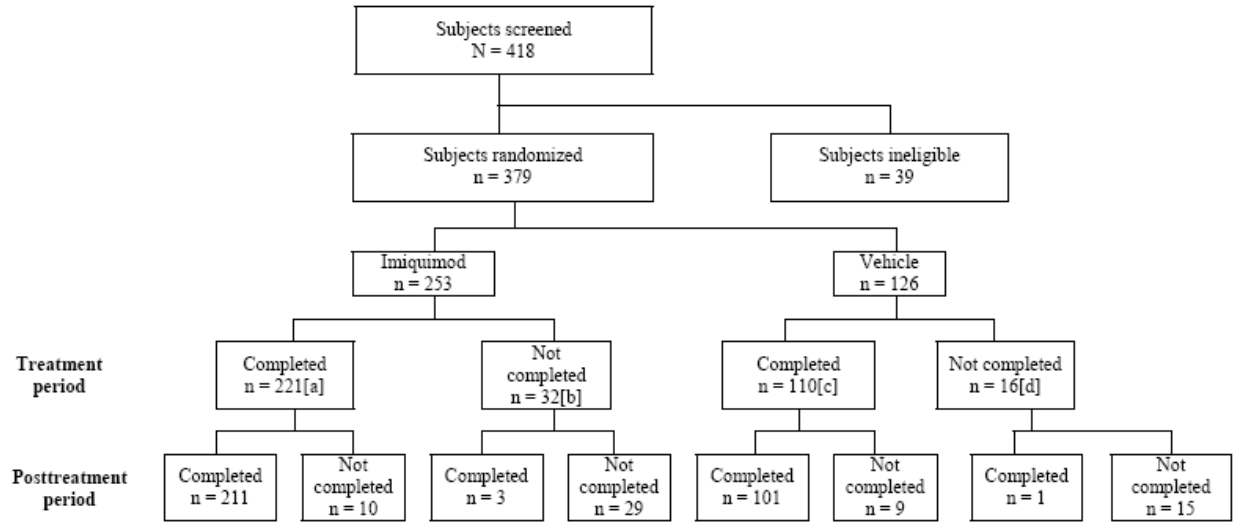


Table 37 Number (%) of Subjects Discontinued During the Treatment Period by Primary Reason

Primary Reason for Discontinuation	(n=253)	(n=126)
TOTAL	32 (13%)	16 (12.7%)
Adverse Event	3 (1%)	1 (1%)
Lost to Follow-up	15 (6%)	6 (5%)
Personal	6 (2%)	3 (2%)
Lack of Therapeutic Effect	5 (2%)	5 (4%)
Other	2 (1%)	1 (1%)
Local Skin Reaction/Sign	1 (<1%)	0 (0%)

Overall, 13% (32/253) and 13% (16/126) of imiquimod and vehicle subjects, respectively, discontinued from the 16-week treatment period. As in Protocol 1494, the most common reason for discontinuation in each treatment group was "lost to follow-up".

A summary of protocol deviations is shown in the following table.

Table 38 Protocol Deviations (Numbers of Subjects)

Departure Code	Imiquimod N=253	Vehicle N=126
Total departures	54	28
Informed consent issues	0	1
Violation inclusion/exclusion criteria	4	0
Study treatment dosing error	22	13
Use of excluded treatments	1	0
Noncompliance with procedures	27	14

A total of 54 (21%) of subjects had protocol violations in the active group compared with 28 (22%) in the vehicle group. The most common type of protocol deviation in each group was dosing error.

Reviewer's comment: The proportions of subjects for whom protocol violations were reported would not likely have had an impact on the overall study results.

Baseline Demographics

Table 39 Baseline Demographics

Variable Description		Imiquimod (n=253)	Vehicle (n=126)
Gender	Female	132 (52%)	77 (61%)
	Male	121 (48%)	49 (39%)
Age at Screening	Median	5	6
	Minimum	2	2
	Maximum	12	12
Height (cm)	Median	114	119
	Minimum	81	89
	Maximum	176	163
Weight (kg)	Median	21	23
	Minimum	11	13
	Maximum	91	56
Race	White	241 (95%)	119 (94%)
	Black/African American	6 (2%)	6 (5%)
	American Indian/Alaska Native	1 (<1%)	0 (0%)
	Asian	3 (1%)	1 (1%)
	Native Hawaiian/Other/ Pacific Islander	2 (1%)	0 (0%)
Ethnicity	Not Hispanic/Latino	227 (90%)	110 (87%)
	Hispanic/Latino	26 (10%)	16 (13%)
Periocular Lesions	Yes	22 (9%)	11 (9%)
	No	231 (91%)	115 (91%)
Atopic Dermatitis	Yes	44 (17%)	24 (19%)
	No	209 (83%)	102 (81%)

Overall, the median age was 5. Most subjects were Caucasian (94%). Approximately 9% of subjects had periocular MC. Across treatment groups, 18% of subjects had atopic dermatitis.

Table 40 Age Distribution

Age Group (years)	Imiquimod (n=253)	Vehicle (n=126)
2 - 3	62 (24%)	26 (21%)
4 - 5	85 (34%)	33 (26%)
6 - 7	47 (19%)	36 (29%)
8 - 9	35 (14%)	19 (15%)
10 - 12	24 (10%)	12 (10%)

Table 41 Number of Baseline MC Lesions

No. of Baseline MC Lesions	Imiquimod (n=253)	Vehicle (n=126)
<5	32 (13%)	19 (15%)
5 - 15	94 (37%)	52 (41%)
16 - 30	65 (26%)	26 (21%)
31 - 50	38 (15%)	17 (14%)
>50	24 (10%)	12 (10%)
Median	16	14
Minimum	2	2
Maximum	148	119
25th Percentile	8.0	6.0
75th Percentile	29.0	29.0

In the imiquimod group, 87% (221/253) had at least 5 MC lesions counted at baseline vs. 85% (107/126) in the vehicle group. The median number of MC lesions at the screening/treatment initiation visit was 16 (range, 2 to 148) for the imiquimod group and 14 (range, 2 to 119) for the vehicle group. There were no meaningful differences in numbers of baseline MC lesions between treatment groups.

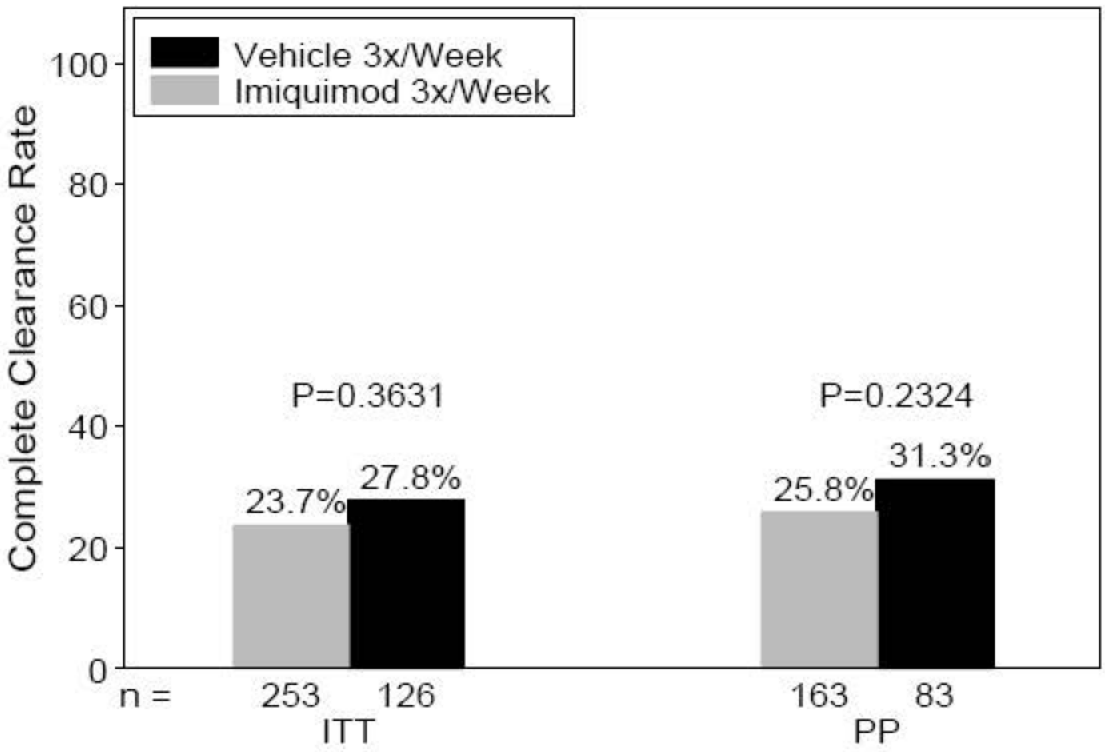
The most common locations for MC lesions during the treatment period were the anterior trunk (70%, 267/379) and lower extremities (57%).

Of the 23 subjects in the imiquimod group with periocular lesions during the treatment period, 22 reported applying study cream in their dosing diary. For vehicle subjects, 11 of the 12 subjects with periocular lesions received study cream as documented in their dosing diary.

Primary Efficacy Analysis:

The complete clearance rates by treatment group for the ITT and PP datasets are shown in the following figure. For the ITT dataset, 24% (60/253) of imiquimod subjects and 28% (35/126) of vehicle subjects achieved complete clearance at the week 18/efficacy assessment visit (p=0.3631).

Figure 3 Complete Clearance Rates at Week 18



Subgroup Analyses:

Table 42 Subgroup Analyses: Complete Clearance at Week 18

Subgroup		Imiquimod	Vehicle
Sex	Female	24% (32/132)	30% (23/77)
	Male	23% (28/121)	24% (12/ 49)
Race	White	23% (56/241)	28% (33/119)
	Nonwhite	33% (4/12)	29% (2/7)
Ethnicity	Hispanic/Latino	12% (3/26)	19% (3/16)
	Not Hispanic/Latino	25% (57/227)	29% (32/110)
Age Group (years)	<4	23% (14/62)	19% (5/26)
	4 - 5	25% (21/85)	27% (9/33)
	6 - 7	15% (7/47)	25% (9/36)
	8 - 9	23% (8/35)	42% (8/19)
	>9	42% (10/24)	33% (4/12)
Periocular Lesions	Yes	4% (1/22)	18% (2/11)
	No	26% (59/231)	29% (33/115)
Atopic Dermatitis	Yes	34% (15/44)	38% (9/24)
	No	22% (45/209)	26% (26/102)
Dosing Compliance	Unknown	0% (0/12)	0% (0/3)
	≥ 100%	25% (19/77)	30% (14/46)
	90 - <100%	19% (13/68)	20% (6/30)
	80 - <90%	31% (12/39)	50% (9/18)
	70 - <80%	25% (5/20)	27% (3/11)
	60 - <70%	47% (8/17)	40% (2/5)
	<60%	15% (3/20)	8% (1/13)
Baseline Erythema	Any	29% (40/140)	31% (19/62)
	None	18% (20/113)	25% (16/64)
MC Duration (months)	Unknown	0% (0/2)	100% (1/1)
	0 - <3	19% (14/73)	12% (5/43)
	3 - <6	28% (13/46)	29% (7/24)
	6 - <12	29% (21/73)	54% (15/28)
	≥12	20% (12/59)	23% (7/30)

No meaningful trends were noted in response rates by MC duration, dosing compliance, presence or absence of atopic dermatitis, periocular location, age, race, ethnicity, or gender.

Table 43 Complete Clearance Rates at Week 18 by Number of Baseline Lesions

Baseline MC Lesion Count	Imiquimod	Vehicle
≤15 MC Lesions	21% (27/126)	28% (20/71)
>15 MC Lesions	26% (33/127)	27% (15/55)

No meaningful differences in response rates were observed in subgroups defined by greater than 15 lesions or by 15 or fewer lesions. Similarly, the week 18 complete clearance rates showed no meaningful trends for absolute difference between (imiquimod – vehicle) by decile of baseline MC lesion count in the ITT dataset (data not shown).

Secondary Efficacy Endpoint

The rates of subjects achieving at least a 50% reduction in the number of MC lesions counted at baseline in all 10 body sites (partial clearance) is shown below.

Table 44 Week 18 Partial Clearance Assessment

	Imiquimod (n=253)	Vehicle (n=126)
Partial Clearance	121 (48%)	63 (50%)
Not Partial Clearance	88 (35%)	42 (33%)
Incomplete Assessment	44 (17%)	21 (17%)

There was no meaningful difference between treatment groups in partial clearance.

Safety:

The extent of exposure is shown in the following table.

Table 45 Extent of Exposure

Total No. of Doses Applied	Imiquimod (n=253)	Vehicle (n=126)
Unknown	12 (5%)	3 (2%)
0 - 6	3 (1%)	2 (2%)
7 - 12	10 (4%)	3 (2%)
13 - 18	7 (3%)	4 (3%)
19 - 24	15 (6%)	8 (6%)
25 - 30	13 (5%)	4 (3%)
31 - 36	29 (12%)	9 (7%)
37 - 42	35 (14%)	18 (14%)
43 - 48	90 (36%)	55 (44%)
>48	39 (15%)	20 (16%)
Median	44	45
Minimum	6	0
Maximum	60	70

The median number of milligrams applied by imiquimod subjects was 588 mg (range, 25 to 1862).

The most frequently reported AE by preferred term was application site reaction, reported in 32% (80/253) of imiquimod subjects and 25% (31/126) of vehicle subjects. Severe application site reactions were the most often reported severe AE, with 5 severe application site reactions experienced by 3 subjects in the imiquimod group and no severe application site reactions occurring in the vehicle group.

The most frequently reported AE by preferred term for subjects with periocular lesions was application site reaction, with 46% (10/22) of imiquimod subjects and 9% (1/11) of vehicle subjects reporting. Conjunctivitis was reported by 2 (9%, 2/22) imiquimod subjects and 0 (0%, 0/11) vehicle subjects with periocular lesions.

Skin quality assessments were made at EOT, week 18, and week 28 visits. The "Most Intense" refers to each subject's most intense skin quality assessment across all treatment sites and study visits and are summarized in the following table.

Table 46 Study 1495: Most Intense Skin Quality Assessments

Skin Quality Variable	Intensity	Imiquimod (n=234)	Vehicle (n=118)
Hyperpigmentation	None	126 (53.8%)	68 (57.6%)
	Mild	77 (32.9%)	36 (30.5%)
	Moderate	31 (13.2%)	12 (10.2%)
	Severe	0 (0.0%)	2 (1.7%)
Hypopigmentation	None	191 (81.6%)	97 (82.2%)
	Mild	35 (15.0%)	15 (12.7%)
	Moderate	7 (3.0%)	6 (5.1%)
	Severe	1 (0.4%)	0 (0.0%)
Scarring	None	171 (73.1%)	89 (75.4%)
	Mild	55 (23.5%)	23 (19.5%)
	Moderate	8 (3.4%)	6 (5.1%)
	Severe	0 (0.0%)	0 (0.0%)
Atrophy	None	201 (85.9%)	100 (84.7%)
	Mild	33 (14.1%)	14 (11.9%)
	Moderate	0 (0.0%)	4 (3.4%)
	Severe	0 (0.0%)	0 (0.0%)

During Study 1495, hyperpigmentation was noted in 46% (108/234) of imiquimod subjects compared to 42% (50/118) of vehicle subjects. Hypopigmentation was noted in 18% (43/234) of imiquimod subjects compared to 18% (21/118) of vehicle subjects. Scarring was noted in 27% (63/234) of imiquimod subjects compared to 25% (29/118) of vehicle subjects. Finally, atrophy was noted in 14% (33/234) of imiquimod subjects compared to 15% (18/118) of vehicle subjects. There did not appear to be meaningful differences between treatment groups in the distribution of maximum intensity for any of these skin quality assessment parameters.

Serious Adverse Events:

One serious adverse event was listed, in subject 0765. The subject had the following events, ear ache, fever, sore throat and vomiting beginning on study day 71 and lasting for 9 days. The subject recovered. The event was deemed not related to study drug.

In study 1495, the median change in systolic blood pressure from baseline to week 8 was 0 mm Hg (mean = 0.7 mm Hg) in the imiquimod group compared to a median change of 0 mm Hg (mean = -2.5 mm Hg) in the vehicle group (p=0.019).

Reviewer's comment: Although there may be a statistically significant change in systolic blood pressure, the median and mean changes in the active treatment arm were very small did not appear to be driven by clinically meaningful differences between treatment groups.

For study 1494: There were no statistically significant differences in changes from baseline between the imiquimod and vehicle groups for any of the vitals signs at any postbaseline visit.

Conclusions:

In terms of efficacy, there was no clinically or statistically significant difference in the clearance rates between imiquimod and placebo.

Five severe application site reactions were reported by 3 imiquimod subjects. The most frequently reported AE considered by the investigator to be probably or possibly related to study cream was application site reaction, with 30% (77/253) of imiquimod and 24% (30/126) of vehicle subjects reporting at least one. The most frequently reported application site reactions reported by imiquimod subjects were erythema at target site (8%, 21/253). Three imiquimod subjects and 1 vehicle subject discontinued treatment due to AEs. One imiquimod subject discontinued during the treatment period due to LSRs.

10.2 Line-by-Line Labeling Review

Below is the draft labeling the FDA accepted on March 22, 2007. Dr. Brenda Carr assisted in the labeling review for the sections related to the FDA-approved indications.

29 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/ TS) immediately following this page

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/s/

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3/22/2007 12:33:07 PM
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Concur with the Clinical Review