

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

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<b>NDA Number:</b>	<b>20-723 (S020)</b>
<b>Submission Date(s):</b>	<b>09/23/06</b>
<b>Brand Name:</b>	<b>Aldara<sup>TM</sup> Cream, 5%</b>
<b>Generic Name:</b>	<b>Imiquimod</b>
<b>Reviewer:</b>	<b>Tapash K. Ghosh Ph.D.</b>
<b>OCPB Division:</b>	<b>DCP3</b>
<b>ORM division:</b>	<b>HFD-540</b>
<b>Sponsor:</b>	<b>3M Pharmaceuticals, St. Paul, MN</b>
<b>Submission Type; Code:</b>	<b>Pediatric Efficacy Supplement</b>
<b>Formulation:</b>	<b>Topical Cream</b>
<b>Indication:</b>	<b>Molluscum Contagiosum</b>

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## **1. Executive Summary**

In this application, 3M submitted an efficacy supplement for the indication of Molluscum Contagiosum (MC) to the above referenced NDA. NDA 20-723 was originally approved for the treatment of external genital and perianal warts on February 27, 1997 by the Division of Antiviral Drug Products. Subsequently it was approved for actinic keratosis (AK) and superficial basal cell carcinoma (sBCC) in adults by the Division of Dermal and Dental Drug Products. This is the first submission geared towards approval of Aldara<sup>TM</sup> Cream, 5% in the pediatric population.

The goal of this efficacy supplement was to obtain safety and efficacy data for the treatment of Molluscum Contagiosum (MC) in children. In this regard, the FDA provided a Written Request to 3M, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act, requesting the evaluation of imiquimod for the treatment of MC in children aged 2 to 12 years. The Written Request outlined 3 studies: 2 phase 3 studies and 1 phase 1 PK study. In this phase I study, a component of the safety assessment included measurement of PK properties of imiquimod in children. This PK study evaluated the systemic exposure of imiquimod in children under maximal use conditions. Subjects who weighed  $\leq 25$  kg applied 1 to 2 packets per dose and subjects who weighed  $> 25$  kg applied 1 to 3 packets per dose. To address the safety concern regarding the potential systemic exposure of children to imiquimod, the PK profile of imiquimod was measured under maximal usage condition predefined by the FDA.

The applicant adequately characterized the pharmacokinetics of imiquimod following single and multiple topical application in pediatric patients with MC. The systemic

exposure data demonstrated that the extent of absorption of imiquimod following topical application to the MC lesional skin of the pediatric subjects was low and comparable to that observed in healthy adults and adults with AK and sBCC.

No safety concern with respect to systemic exposure of imiquimod and/or its metabolites was noted. However, the sponsor failed to demonstrate efficacy of the Aldara™ Cream, 5% in pediatric patients with MC.

### **Efficacy and Safety 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). In both studies, 24% of Aldara treated patients experienced complete clearance compared with 26% and 18% in Vehicle-treated patients, in studies 1494 and 1495, respectively. According to the sponsor and the clinical reviewer, neither of the phase 3 clinical studies demonstrated efficacy of Aldara for the treatment of MC. The response rate was slightly higher in the vehicle-treated arms in both studies compared with the Aldara group. In conclusion, Efficacy was not established in these studies.

According to the clinical reviewer, no deaths, SAEs, or other significant AEs were reported during the study. Local skin reactions were generally more intense at the end of the 4-week treatment period compared with baseline. A decrease in WBC, absolute neutrophil, and absolute lymphocyte counts as well as a decrease in the percentage of neutrophils composing the WBC differential was observed in some subjects following treatment with imiquimod. According to the sponsor, none of these changes were considered clinically relevant.

### **1.1 Recommendation**

Based on the data submitted in NDA 20-723 (S020), the application is acceptable from a clinical pharmacology perspective.

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Tapash K. Ghosh, Ph.D.  
Clinical Pharmacology Reviewer  
Division of Clinical Pharmacology 3; Office of Clinical Pharmacology

### **Concurrence:**

**Hae-Young Ahn, Ph.D.**  
Deputy Director, Division of Clinical Pharmacology 3  
FDA/CDER/OCF/DCP3

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## 3. Review:

Molluscum contagiosum is a common childhood viral infection with cutaneous manifestations characterized by firm, umbilicated dome-shaped papules ranging in size from 1 mm to 1 cm. Most patients typically present with multiple MC lesions, with the trunk, axillae, antecubital and popliteal fossae, and crural folds being the most common anatomical locations.

Aldara™ (imiquimod 5% cream) is approved for use in children  $\geq 12$  years for the treatment of external genital/perianal warts (EGW). Children  $< 12$  years of age are often treated with Aldara despite the absence of adequate pediatric safety data, potentially resulting in age-specific adverse reactions not previously observed in adults. The percutaneous absorption and systemic exposure to single or multiple topical doses of imiquimod in adults has been shown to be minimal. Because systemic exposure to imiquimod in pediatric subjects with MC has not been studied, the safety margins in this population may differ from those in adults. The systemic exposure to imiquimod in children with MC lesions covering a large BSA may be higher than previously observed in adult subjects with EGW and AK. Therefore, this study evaluated the systemic exposure and safety of imiquimod in children with extensive MC.

To obtain safety and efficacy data for the treatment of MC in children, the FDA provided a Written Request to 3M, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act, requesting the evaluation of imiquimod for the treatment of MC in children aged 2 to 12 years. The Written Request outlined 3 studies: 2 phase 3 studies and 1 phase I PK study. The phase 3 studies (1494-IMI and 1495-IMI) were completed in 2005. The Written Request required that in this phase I PK study, the children enrolled should be about equally distributed across the entire 2 to 12 years age range. In this phase I study, a component of the safety assessment included measurement of PK properties of imiquimod in children. The percutaneous absorption and the systemic exposure to single or multiple topical doses of imiquimod in adults has been shown to be minimal. However, extrapolating pediatric safety margins from information on adults has its limitations. The systemic exposure to imiquimod in children with MC lesions covering a large BSA may be higher than previously observed in adult subjects with EGW or AK.

The FDA Written Request required that subjects apply imiquimod to at least 10% of each subject's total BSA (as determined using a modified Lund-Browder chart) to evaluate maximal use conditions. During the screening visit, children with MC were evaluated for the number of MC lesions on their bodies, with the exception of eyelids, hands, and, if

the subject wore diapers, the inguinal region and buttocks. Treatment areas were designated and the relative percent of total BSA of treatment area(s) was calculated. Because MC can involve extensive BSA in some children, this PK study evaluated the systemic exposure of imiquimod in children under maximal use conditions. Subjects who weighed  $\leq 25$  kg applied 1 to 2 packets per dose and subjects who weighed  $>25$  kg applied 1 to 3 packets per dose. To address the safety concern regarding the potential systemic exposure of children to imiquimod, the PK profile of imiquimod was measured after applying study cream to the treatment area(s). Once each subject's treatment area(s) were designated at the treatment initiation visit, the treatment area(s) and amount of study drug applied at each dose remained consistent throughout the treatment period.

#### **4. Labeling Language:**

**Sponsor's:** Systemic absorption of imiquimod across the affected skin of 22 patients aged 2 to 12 years with extensive molluscum contagiosum (MC) was observed at a dosing frequency of 3 applications per week for 4 weeks. Extensive disease was defined as MC lesion treatment area (s) involving at least 10% of the total body surface area (BSA). Mean peak serum drug concentrations at the end of week 4 were  $< 3$  ng/ml for all age ( $\leq 5$  and  $>5$  years) and dose groups (1, 2 or 3 packets). Systemic exposure in pediatric patients was similar to that seen in adults with AK administered Aldara Cream at approximately the same dose when normalized for body weight.

**Reviewer's:** Systemic absorption of imiquimod across the affected skin of 22 patients aged 2 to 12 years with extensive MC involving at least 10% of the total body surface area was observed after single and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. The investigator determined the dose applied, either 1, 2 or 3 packets per dose, based on the size of the treatment area and the subject's weight. The overall median peak serum drug concentrations at the end of week 4 was between 0.26 and 1.06 ng/ml except in a 2-year old female who was administered 2 packets of study drug per dose, had a Cmax of 9.66 ng/mL after multiple dosing. Among the 20 (b) (4) with evaluable laboratory assessments, the median WBC count decreased by  $1.4 \times 10^9$  /L and the median absolute neutrophil count decreased by  $1.42 \times 10^9$  /L.

#### **5. Individual Study Report:**

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**NDA:** 20-723 (S020)/Study 1498-IMIQ

**Study Date:** Jul 2004 – Apr 2006

#### **Phase I Pharmacokinetic Study of Imiquimod Cream, 5% in Pediatric Subjects with Molluscum Contagiosum**

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**Objective:** The primary objective was to evaluate the systemic exposure of imiquimod following single- and multiple-dose administration in pediatric subjects aged 2 to 12 years with extensive MC. Secondary objectives included the evaluation of safety and tolerance of topically applied imiquimod in pediatric subjects with extensive MC disease.

**Methods:** This was an open-label, multicenter study that evaluated single and multiple applications of imiquimod applied topically 3 times per week (3x/wk) for 4 weeks to the entire MC lesion treatment area(s) in pediatric subjects aged 2 to 12 years.

Eligible subjects were required to have MC treatment area(s) on the head, neck, trunk, extremities, or buttocks (if area was not occluded by diapers or training pants) that involved  $\geq 10\%$  of the total body surface area (BSA). 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  $\leq 25$  kg applied 1 or 2 packets of Imiquimod cream, 5%; while subjects who weighed  $> 25$  kg applied 1 to 3 packets (Lot Nos. PD-03-11883 or PD-05-12674 (U-2e formulation)).

At the treatment initiation visit, each treatment area was recorded on a standardized body diagram. Subjects reported to the clinic at treatment week 2 for safety assessments and week 4 for end-of-study (EOS) procedures. At each treatment period visit, safety procedures were performed and the subject's diary was reviewed for dosing compliance.

Each subject participated in two 10-hour clinic visits (treatment initiation and week 4/EOS visits), during which blood samples were collected at predose and at 2, 4, and 8 hours postdose to determine systemic drug exposure after single and multiple-dose administrations of study cream. 15 evaluable subjects were planned; 22 subjects with the following baseline characteristics were enrolled in order to obtain at least 15 subjects who finished the study and produced evaluable data.

Baseline Demographic Characteristics (ITT)

Variable Description	Statistic/ Level	Imiquimod 3x/Week (n=22)
Subject's Sex	Female	8 ( 36.4%)
	Male	14 ( 63.6%)
Age Group	<= 5	9 ( 40.9%)
	> 5	13 ( 59.1%)
Race	White	20 ( 90.9%)
	American Indian/Alaska Native	1 ( 4.5%)
	Asian	1 ( 4.5%)
Ethnicity	Not Hispanic/Latino	20 ( 90.9%)
	Hispanic/Latino	2 ( 9.1%)
Age (years)	N	22
	MEAN	6.2
	SD	2.87
	MEDIAN	6.0
	MIN	2
	MAX	12
Height (cm)	N	21
	MEAN	123.2
	SD	17.19
	MEDIAN	125.0
	MIN	90
	MAX	151
Weight (kg)	N	22
	MEAN	26.3
	SD	9.74
	MEDIAN	24.5
	MIN	14
	MAX	47

Percentage of Body Surface Area with MC Treatment Areas (ITT)

Visit	n	Mean	Standard Deviation	Median	Minimum	Maximum
Screening	22	14.7%	7.44%	12.1%	10.0%	43.7%
Initiation - Predose	21	14.6%	4.30%	13.5%	10.0%	22.9%

Pediatric patients 2- 12 yeas old were about equally distributed across the entire age range [ $\leq 5$  yrs (n=9, 40.9%);  $> 5$  yrs (n=13, 59.1%)] as described in the following table.

Age Distribution (ITT)	
Age Group (years)	Imiquimod 3x/Week (n=22)
2 - 4	8 ( 36.4%)
5 - 6	4 ( 18.2%)
7 - 8	5 ( 22.7%)
9 - 10	3 ( 13.6%)
11 - 12	2 ( 9.1%)

**Pharmacokinetics:** PK measurements consisted of serum drug concentration measurements of imiquimod and 2 metabolites after doses 1 and 12 (final dose) to calculate the C<sub>max</sub>, T<sub>max</sub>, and AUC after single and multiple doses. The primary analyte was serum imiquimod, and the primary PK variables were C<sub>max</sub> and AUC.

Pharmacokinetic data were tabulated and descriptive summary statistics were provided for all PK parameters after the first and last dose, stratified by age (2 to 5 years and 6 to 12 years), by percent BSA treated (<15% BSA and ≥15% BSA), and for all subjects pooled (2 to 12 years).

Correlation coefficients between the imiquimod PK variables (C<sub>max</sub> and AUC) and the dosage (mg/kg and mg/m<sup>2</sup>), and between the imiquimod PK variables and the percent BSA treated per dose level (i.e., the number of packets applied) were determined after single and multiple dosing.

**Efficacy:** No formal efficacy measurements were performed in this study; however, total MC lesion clearance within the treatment area(s) was assessed by visual and tactile examinations at the week 4/EOS visit.

**Safety:** Safety was assessed throughout the study by monitoring adverse events (AEs), local skin reactions (LSRs) (erythema, edema, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting), vital signs measurements, and concomitant medication use. Physical examinations, photographs of treatment area(s), and routine chemistry and hematology tests were also performed.

## **Results:**

### **Bioanalytical Methods Validation:**

Serum concentrations of imiquimod (aka, R-837) and the 2 combined metabolites, S-26704/S-27700, were measured at 3M between 19 August 2004 and 05 May 2006 following the procedures described in validated Bioanalytical Method 9196.91. The analytes (imiquimod, S-26704/S-27700, and internal standard) were prepared for analysis by an organic solvent protein precipitation procedure. Analyses of imiquimod and S-

26704/S-27700 in the sample preparations were performed using liquid chromatography coupled with triple-quadrupole mass spectrometry (LC/MS/MS).

The linear range of the assay was 0.0500 to 10.0 ng/mL of imiquimod and S-26704/S-27700 using 0.100 ml of human serum. The back-calculated value for each acceptable calibration standard was within  $\pm 15\%$  ( $\pm 20\%$  at the lower limit of quantitation) of the nominal value for the standard.

The inter-day precision and accuracy were calculated from the analysis results of the QC samples run during the course of the study for the 10 analytical runs. The inter-day percent coefficient of variation (CV%) and percent relative error are summarized in the following Tables.

#### Summary of Human Serum Imiquimod Quality Control Results

Theoretical Imiquimod Concentration	n	Inter-day Mean (ng/mL)	Inter-day CV%	Inter-day RE%
0.150 ng/mL (Low-QC)	20	0.147	8	-2.0
1.50 ng/mL (Mid-QC)	20	1.54	8	2.7
8.00 ng/mL (High-QC)	20	8.71	8	8.9
80.0 ng/mL (Dilution-QC)	3	76.8	2	-4.0

Abbreviations: CV%=percent coefficient of variation, QC=quality control, RE%=percent relative error

#### Summary of Human Serum S-26704/S-27700 Quality Control Results

Theoretical Imiquimod Concentration	n	Inter-day Mean (ng/mL)	Inter-day CV%	Inter-day RE%
0.150 ng/mL (Low-QC)	12	0.151	9	0.7
1.50 ng/mL (Mid-QC)	12	1.55	8	3.3
8.00 ng/mL (High-QC)	12	8.33	6	4.1
80.0 ng/mL (Dilution-QC)	NA	NA	NA	NA

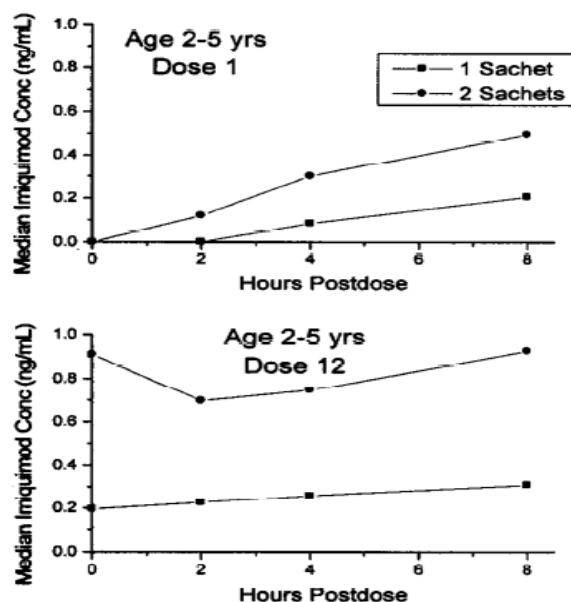
Abbreviations: CV%=percent coefficient of variation, NA=not applicable, QC=quality control, RE%=percent relative error

#### Pharmacokinetic Results:

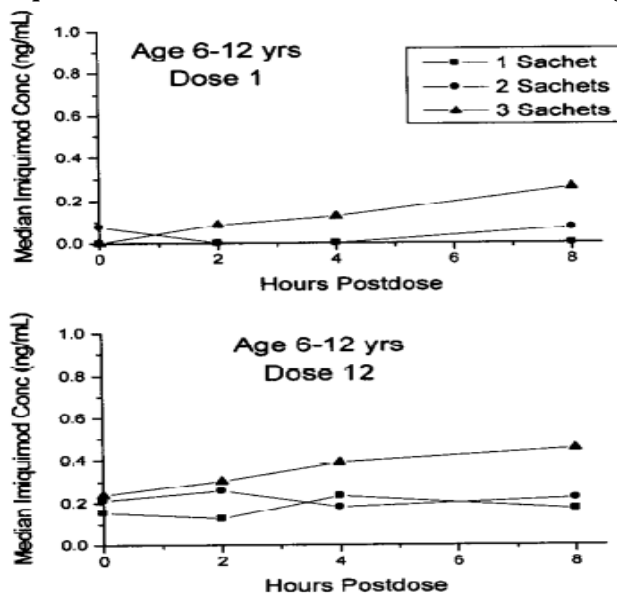
After a *single-dose* application of imiquimod, low but measurable concentrations of imiquimod ( $<1.3$  ng/mL) were detected in the serum of 91% (20/22) of subjects. For most subjects, concentrations tended to increase steadily throughout the 8-hour collection interval to a maximum at 8-hour postdose. After *multiple dosing*, measurable concentrations of imiquimod were observed in the predose (trough) serum collected just prior to the last dose in all subjects, ranging in concentration from 0.130 to 1.69 ng/mL. From that time point throughout the 8-hour collection interval, the serum concentration-time profiles for most subjects generally had little fluctuation in the serum imiquimod concentrations (Figure 1 and Figure 2).

**Fig 1: Median Serum Imiquimod Concentration versus Time Profiles for Subjects Age 2 to 5 Years**





**Fig 2: Median Serum Imiquimod Concentration versus Time Profiles for Subjects Age 6 to 12 Years**



Maximum systemic concentrations of imiquimod following single and multiple-dose (3x/wk for 4 weeks) administration of imiquimod 5% cream in pediatric subjects aged 2 to 12 years with extensive MC ( $\geq 10\%$  BSA) were low. Median  $C_{max}$  values were  $\leq 0.5$  ng/mL after a single dose (Table 1) and  $\leq 1$  ng/mL after multiple dosing (Table 2). Only 9% (2/22) of subjects after a single dose, and 18% (4/22) of subjects after multiple dosing had  $C_{max}$  values  $>1$  ng/mL, all of which were in the 2- to 5-year old age group after receiving 2 packets of imiquimod cream (Table 1 and 2). Three (3) of those 4 subjects had  $C_{max}$  values of  $<1.7$  ng/mL. One subject (Subject No. 0004/0051), a 2-year old female who was administered 2 packets of study drug per dose, had a  $C_{max}$  of 9.66 ng/mL after multiple dosing. This was at least 6-times higher than the maximum concentration observed in any other subject at the same dose. Systemic exposure, measured as AUC(0-8), generally agreed well with the  $C_{max}$  results.

**Table 1: Median Serum Imiquimod Pharmacokinetic Parameters after a Single Topical Application of Imiquimod Cream, 5% – Stratified by Age**

Age Group	Number Packets	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC(0-8) (ng·hr/mL)
2-5 yrs	1	0.205 (n=2)	7.97 (n=1)	0.710 (n=2)
6-12 yrs	1	0.0852 (n=3)	5.04 (n=2)	0.0878 (n=3)
2-5 yrs	2	0.495 (n=7)	8.00 (n=7)	2.33 (n=7)
6-12 yrs	2	0.148 (n=2)	3.99 (n=2)	0.257 (n=2)
2-5 yrs	3	[a]	[a]	[a]
6-12 yrs	3	0.308 (n=8)	8.00 (n=8)	1.29 (n=8)

Abbreviations: AUC(0-8)=area under the serum concentration curve from time zero (0) through 8 hours postdose, C<sub>max</sub>=maximum drug concentration, T<sub>max</sub>=time to maximum drug concentration, yrs=years

[a] No subjects in this age group received 3 packets.

**Table 2: Median Serum Imiquimod Pharmacokinetic Parameters after Multiple Topical Applications of Imiquimod Cream, 5% – Stratified by Age**

Age Group	Number Packets	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC(0-8) (ng·hr/mL)
2-5 yrs	1	0.309 (n=2)	8.12 (n=2)	2.08 (n=2)
6-12 yrs	1	0.267 (n=3)	3.97 (n=3)	1.55 (n=3)
2-5 yrs	2	1.06 (n=7)	4.00(n=7)	7.01 (n=7)
6-12 yrs	2	0.261 (n=2)	1.09 (n=2)	1.70 (n=2)
2-5 yrs	3	[a]	[a]	[a]
6-12 yrs	3	0.567 (n=8)	4.01 (n=8)	3.18 (n=8)

Abbreviations: AUC(0-8)=area under the serum concentration curve from time zero (0) through 8 hours postdose, C<sub>max</sub>=maximum drug concentration, T<sub>max</sub>=time to maximum drug concentration, yrs=years

[a] No subjects in this age group received 3 packets.

In general, systemic exposure tended to be higher after multiple dosing compared to that after a single dose with dose 12:dose 1 C<sub>max</sub> and AUC ratios consistently showing as increase in both PK parameters after multiple dosing (Table 3). These observations, together with the measurable serum predose values detected in all subjects after multiple dosing, suggest an increase in penetration and/or accumulation of imiquimod occurred in the systemic circulation when administered to pediatric subjects at a frequency of 3x/wk for 4 weeks. Assuming C<sub>max</sub> to be a more accurate measure of the extent of change in exposure than the partial AUC, there was about 2- to 3.5-times increase in penetration and/or accumulation following multiple dosing.

**Table 3: Comparison of Single vs Multiple Dose Pharmacokinetics**

Age Group	Number Packets	Median Cmax Ratio (Dose 12/Dose 1)	Median AUC Ratio (Dose 12/Dose 1)
2-5 yrs	1	0.9 (n=1)	1.8 (n=1)
6-12 yrs	1	2.7 (n=2)	11.5 (n=2)
2-5 yrs	2	3.4 (n=7)	5.2 (n=7)
6-12 yrs	2	1.8 (n=2)	4.1 (n=1)
2-5 yrs	3	[a]	[a]
6-12 yrs	3	2.3 (n=8)	2.9 (n=8)

Abbreviations: AUC=area under the serum concentration curve, Cmax=maximum drug concentration, yrs=years

[a] No subjects in this age group received 3 packets.

To determine if there was a relationship between systemic exposure to imiquimod and body surface area, descriptive statistics were also done on the PK parameters stratified by the percent BSA treated (<15% BSA and ≥15% BSA). No correlation was observed directly between either of the PK parameters (Cmax or AUC) and the percent BSA treated, with p-values ranging from 0.2 to 0.9 for these correlations. There was also no correlation between either PK parameter and the dose when normalized for total BSA (mg/m<sup>2</sup>) with p-values of 0.5 after a single dose and 0.1 after multiple dosing for both Parameters.

Systemic concentrations of the 2 combined metabolites, S-26704 and S-27700, were below the lower limit of quantitation (<0.0500 ng/mL) in most subjects after the first dose. Only 5 of 22 subjects had measurable concentrations of S-26704/S-27700 in their serum, 4 of which were in the 2- to 5-year old age group after applying 2 packets of imiquimod cream, all of them with concentrations of ≤0.1 ng/mL.

After multiple dosing, serum S-26704/S-27700 concentrations remained below the lower limit of quantitation in most subjects (11/13) in the 6- to 12-year old age group. In the 2- to 5-year old age group, 6 of 9 subjects had measurable concentrations of metabolites in their serum after multiple dosing consistent with increased concentrations of imiquimod after multiple dosing in the same subjects. All 6 of those subjects were administered 2 packets of drug. The highest individual serum S-26704/S-27700 concentration measured in this study was 0.230 ng/mL in Subject No. 0004/0051 (a 2-year old white female with approximately 14% BSA with MC) at 8 hours following administration of the last dose. This was also the same subject who had the highest concentration of imiquimod (9.66 ng/mL) in her serum. In all but 1 case, S-26704/S-27700 concentrations were only measurable in the serum of subjects who had imiquimod concentrations of ≥0.5 ng/mL in their serum.

## Efficacy Conclusions

For the ITT dataset, the complete clearance rate at the week 4/EOS visit was 0% (0/22). None of the 22 subjects enrolled in this study completely cleared their MC lesions during the study.

## Pharmacokinetics Conclusions

Peak serum concentrations of imiquimod following single and multiple-dose administration of imiquimod in pediatric subjects aged 2 to 12 years with extensive MC ( $\geq 10\%$  BSA) were low ( $<10$  ng/mL). Similar peak concentrations were seen in adults administered topical imiquimod at approximately the same dose when normalized for body weight. In addition, there were little ( $<0.3$  ng/mL) or no systemic concentrations of the combined metabolites, S-26704/S-27700. With multiple dosing, the PK data suggest there was about a 2- to 3.5-times increase in penetration and/or accumulation of imiquimod in the systemic circulation when administered to pediatric subjects at a frequency of 3x/wk for 4 weeks.

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 olds administered 2 packets of cream. Within the age groups, systemic exposure to imiquimod tended to increase with increasing dose, where dose was measured as the number of packets applied. When the dose was normalized for body weight (assuming 12.5 mg of imiquimod per packet) regardless of age, significant correlations were observed between the imiquimod PK parameters [ $C_{max}$  and  $AUC(0-8)$ ] and the dosage (mg/kg) after both single and multiple dosing. No correlation was seen between either PK parameter and the percent BSA treated or the dose normalized for total BSA (mg/m<sup>2</sup>).

## Discussion and Overall Conclusions

The low systemic concentrations of imiquimod measured in this study support the safety of 3x/week dosing in children. Other safety evaluations (including LSR assessments, reports of serious and significant AEs, and laboratory abnormalities) reported in this study are consistent with those reported from the 1494-IMI and 1495-IMI phase 3 studies and support 3x/week dosing in children. While decreases in some WBC parameters were observed in a few subjects, none of the changes were clinically meaningful. Changes in these laboratory parameters have been previously observed during adult clinical studies; therefore, it is not unexpected that these changes would also be observed in the pediatric population applying up to 3 packets of imiquimod 5% cream over a large BSA.

In conclusion, peak serum concentrations of imiquimod following single and multipledose administrations of up to 3 packets/dose in pediatric subjects aged 2 to 12 years with extensive MC ( $\geq 10\%$  BSA) were low ( $<10$  ng/mL), similar to what was seen in adults administered topical imiquimod at approximately the same dose when normalized for body weight.

## Comments:

*The highest individual serum S-26704/S-27700 concentration measured in this study was 0.230 ng/mL in Subject No. 0004/0051 (a 2-year old white female with approximately 14% BSA with MC) at 8 hours following administration of the last dose. This was also the same subject who had the highest concentration of imiquimod (9.66 ng/mL) in her*

*serum. The patient's case history did not reveal any mitigating factor that caused that high systemic exposure. Though due to lack of observed efficacy in the pediatric MC population, Aldara will not be recommended to be prescribed in pediatric population, this information, however, will be reported in the revised label to caution prescribers that young skin may occasionally show relatively high systemic exposure.*

CC: NDA 20-723, HFD-540 (M. Owen)

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/s/

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