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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señor

DIRECTOR DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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REF: Expediente No. **11-087690**– solicitud de patente de invención a favor de **GRACEWAY PHARMACEUTICALS, LLC**. Título **FORMULACIONES DE IMIQUIMOD DE BAJA CONCENTRACIÓN DE DOSIS Y REGIMENES DE DOSIS DE CORTA DURACIÓN PARA TRATAR QUERATOSIS ACTÍNICA**

RESPUESTA A OPOSICIÓN

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante me permito dar respuesta a la oposición presentada por **SYNTHESIS S.A.S.**, relacionada con la patentabilidad de la presente invención y notificado por fijación en lista el 27 de Julio de 2012.

La presente invención se refiere a formulaciones farmacéuticas tópicas de 1-isobutil-1H-imidazo[4,5-c]-quinolin-4-amina, también conocido como imiquimod, las cuales se caracterizan por ser formuladas con una menor concentración de principio activo, presentar un perfil de seguridad mejorado, y además requerir una administración de menor duración en comparación con las composiciones de imiquimod al 5% comercialmente disponibles, tales como Aldara®, lo cual no se encuentra contemplado por el arte previo, y se constituye en una ventaja sobre el mismo.

Por otra parte, de acuerdo con las modificaciones realizadas sobre el pliego reivindicatorio, el argumento mediante el cual el señor Opositor establece que "las reivindicaciones se refieren métodos terapéuticos y no solo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible, y según la legislación solo serán patentables los productos o procedimientos.

Por lo tanto a la luz de la norma, dicha materia referente a métodos terapéuticos no sería patentable”, pierde toda validez, toda vez que el nuevo pliego reivindicatorio se encuentra dirigido a revelar composiciones farmacéuticas de imiquimod al 2.5% y 3.75%, es decir, productos, y por tanto la materia reivindicada es plenamente patentable de acuerdo con los lineamientos de la Decisión 486.

Así, el nuevo pliego reivindicatorio se encuentra dirigido a una composición tópica de imiquimod, en donde la composición comprende imiquimod en una cantidad de 2,5% o 3,75% en peso, junto con un vehículo farmacéuticamente aceptable que comprende un ácido graso, en donde la composición está en forma de una crema.

Ahora bien, el señor Opositor establece que la referencia US2008280943 se refiere a paquetes farmacéuticos y métodos para mejorar la seguridad del imiquimod cuando se utiliza para tratar a los niños afectados por trastornos de la piel, y que dicho documento enseña un método de tratamiento de un sujeto con queratosis actínica, en donde el método comprende aplicar una dosis de fuerza menor de la formulación de imiquimod una vez al día, por lo cual considerar el señor Opositor que dicha referencia afecta la novedad de la presente invención.

Al respecto, la referencia en mención no enseña ni sugiere dentro de su contenido composiciones de imiquimod que contengan 2.5% y 3.75% en peso del principio activo, y menos aún, que composiciones con dichas características presenten las ventajas encontradas por los inventores, al tener en cuenta que el arte previo solo contempla las composiciones de imiquimod al 5%, y es a las mismas a las que atribuye el efecto farmacológico de utilidad en el tratamiento de la afecciones dermatológicas.

Con el fin de dar evidencia de las ventajas de la presente invención, nos permitimos incluir los resultados obtenidos al comparar la información contenida en el inserto del producto Aldara® (Imiquimod al 5 %) y en un artículo de los inventores publicado en el Journal de la Academia Americana de Dermatología que corresponde a un estudio clínico que evalúa las composiciones de imiquimod al 2.5% y 3.75 %, en donde además se establece que las composiciones de imiquimod a dichas concentraciones son aptas para ser aplicadas en superficies sensibles, tales como la piel del rostro, y más importante aún que las composiciones de la presente invención son más toleradas, en términos de la posibilidad de aplicación en áreas de la piel más extensas y la asociación con la presentación de eventos adversos asociados con su administración, en comparación con las composiciones conocidas al 5%.

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La siguiente tabla resume los resultados encontrados en cuanto a la presentación de un evento adverso asociado a la aplicación tópica de imiquimod.

<i>Evento adverso: Pacientes que reportaron prurito en el sitio de aplicación (%)</i>			
Composición	5% ⁽¹⁾	2.5% ⁽²⁾	3.75% ⁽²⁾
Esquema de tratamiento	16-semanas	2x2x2	2x2x2
No. Pacientes que presentaron evento	20	3.8	4.4
⁽¹⁾ Inserto Aldara; ⁽²⁾ N. Swanson <i>et al.</i> , <i>J. Am. Acad. Dermatol.</i> , 62: 582-590 (2010)			

En dicha tabla, el evento adverso prurito fue reportado solo por un 4% de los pacientes a los cuales les fueron administradas las composiciones de imiquimod al 2.5% y al 3.75%, mientras que en contraste un 20% de los pacientes a los cuales les fue administrada la composición de imiquimod al 5%, conocida en el arte previo, reportaron el evento adverso en mención.

Así las cosas, los inventores de la presente invención establecieron que las composiciones de imiquimod al 2.5% y al 3.75% en peso del principio activo presentan una eficacia equiparable con la presentada por las composiciones al 5% pero con un perfil de tolerancia mejorado, lo cual en definitiva es una ventaja sobre el arte previo.

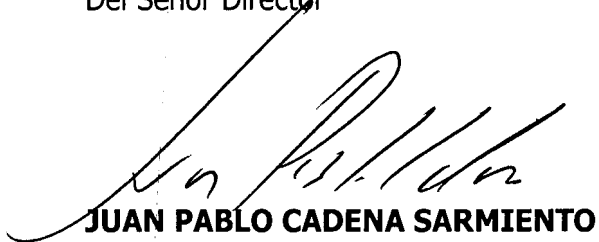
En este orden de ideas, la presente invención reclama como novedosas e inventivas composiciones de imiquimod a concentraciones de 2.5 y 3.75 % no contempladas por el arte previo, las cuales sorprendentemente muestran una eficacia similar a las composiciones de mayor concentración y presentan un perfil de seguridad mejorado, en términos de mayor tolerancia y baja presentación de eventos adversos, lo cual la hace novedosa e inventiva frente al estado del arte, y por tanto la misma es plenamente patentable de acuerdo a las disposiciones de la Decisión 486.

Finalmente, deseamos presentar a su consideración un nuevo pliego reivindicatorio compuesto por 41 reivindicaciones el cual se encuentra en la respuesta a la oposición presentada por LAFRANCOL S.A.

Anexos

- a. Inserto ALDARA®
- b. Estudio inventores Imiquimod

Del Señor Director



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.SJ.

C.C. 80.410.337 de Usaquén

Calle 70 A No. 4 - 41

NDA 20-723/S-011

NDA 20-723/S-012

TEXT OF THE LABELING FOR THE DRUG

Revised Package Insert

ALDARA™

[al dar' a]

(imiquimod)

Cream, 5%

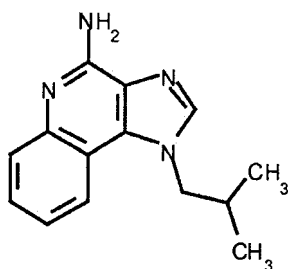
For Dermatologic Use Only -

Not for Ophthalmic Use.

DESCRIPTION

Aldara™ is the brand name for imiquimod which is an immune response modifier. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

Chemically, imiquimod is 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine. Imiquimod has a molecular formula of C₁₄H₁₆N₄ and a molecular weight of 240.3. Its structural formula is:



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CLINICAL PHARMACOLOGY

Pharmacodynamics

Imiquimod has no direct antiviral activity in cell culture. A study in 22 patients with genital/perianal warts comparing imiquimod and vehicle shows that imiquimod induces mRNA encoding cytokines including interferon- α at the treatment site. In addition HPV L1 mRNA and HPV DNA are significantly decreased following treatment. However, the clinical relevance of these findings is unknown.

Pharmacokinetics

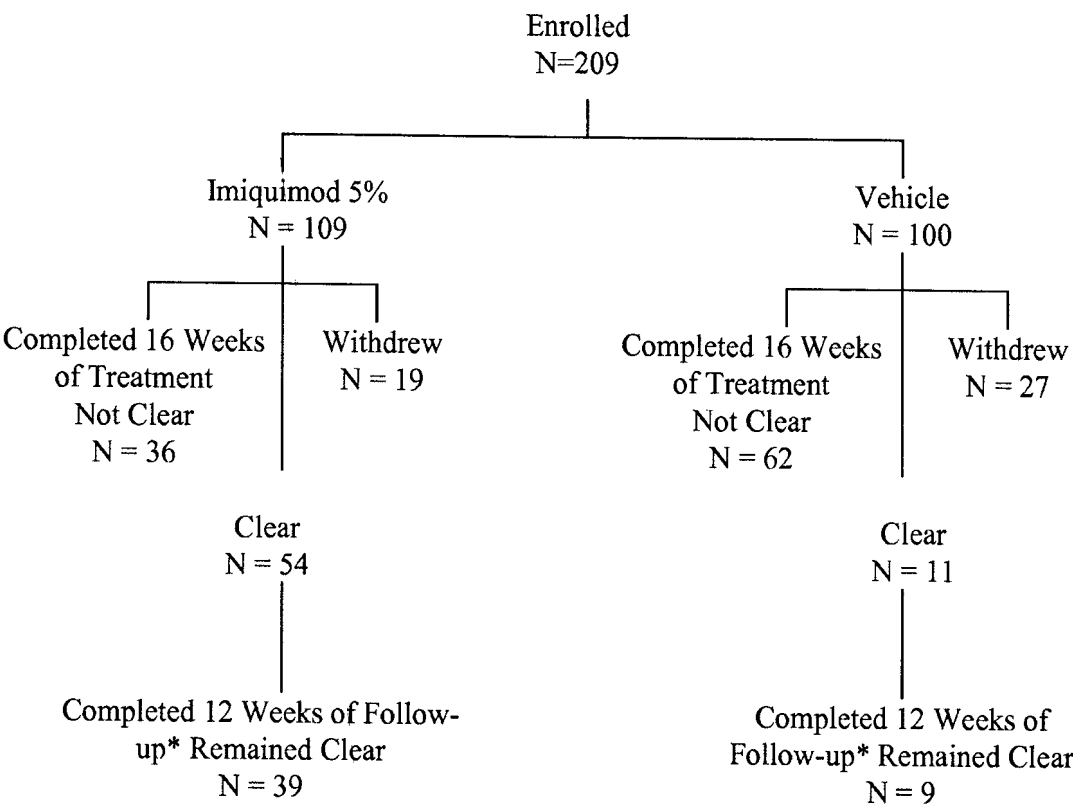
Percutaneous absorption of [^{14}C] imiquimod was minimal in a study involving 6 healthy subjects treated with a single topical application (5 mg) of [^{14}C] imiquimod cream formulation. No radioactivity was detected in the serum (lower limit of quantitation: 1 ng/mL) and < 0.9% of the radiolabelled dose was excreted in the urine and feces following topical application.

CLINICAL STUDIES

In a double-blind, placebo-controlled clinical trial, 209 otherwise healthy patients 18 years of age and older with genital/perianal warts were treated with Aldara 5% cream or vehicle control 3X/week for a maximum of 16 weeks. The median baseline wart area was 69 mm² (range 8 to 5525 mm²). Patient accountability is shown in the figure below.

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1004-IMIQ Patient Accountability



* The other patients were either lost to follow-up or experienced recurrences.

Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.

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CLEARANCE - STUDY 1004

	Treatment	Patients with Complete Clearance of Warts	Patients Without Follow-up	Patients with Warts Remaining at Week 16
Overall	imiquimod 5% (n=109)	50%	17%	33%
	vehicle (n=100)	11%	27%	62%
Females	imiquimod 5% (n=46)	72%	11%	17%
	vehicle (n=40)	20%	33%	48%
Males	imiquimod 5% (n=63)	33%	22%	44%
	vehicle (n=60)	5%	23%	72%

INDICATIONS AND USAGE

Aldara 5% cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years old and above.

CONTRAINDICATIONS

None known

WARNINGS

Aldara cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and is not recommended for these conditions.

PRECAUTIONS

General

Local skin reactions such as erythema, erosion, excoriation/flaking, and edema are common.

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Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with Aldara cream can be resumed after the skin reaction has subsided. There is no clinical experience with Aldara cream therapy immediately following the treatment of genital/perianal warts with other cutaneously applied drugs; therefore, Aldara cream administration is not recommended until genital/perianal tissue is healed from any previous drug or surgical treatment. Aldara has the potential to exacerbate inflammatory conditions of the skin.

Information for Patients

Patients using Aldara 5% cream should receive the following information and instructions. The effect of Aldara 5% cream on the transmission of genital/perianal warts is unknown. Aldara 5% cream may weaken condoms and vaginal diaphragms. Therefore, concurrent use is not recommended.

1. This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided.
2. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
3. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.
4. It is recommended that 6-10 hours following Aldara 5% cream application the treatment area be washed with mild soap and water.
5. It is common for patients to experience local skin reactions such as erythema, erosion, excoriation/flaking, and edema at the site of application or surrounding areas. Most skin reactions are mild to moderate. Severe skin reactions can occur and should be reported promptly to the prescribing physician.
6. Application of Aldara cream in the vagina is considered internal and should be avoided. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can result in pain or swelling, and may cause difficulty in passing urine.
7. Some reports have been received of localized hypopigmentation and hyperpigmentation following Aldara use. Follow-up information suggests that these skin color changes may be permanent in some patients.
8. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

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9. Patients should be aware that new warts may develop during therapy, as Aldara is not a cure.

Carcinogenicity, Mutagenesis, and Impairment of Fertility

Rodent carcinogenicity data are not available. Imiquimod was without effect in a series of eight different mutagenicity assays including Ames, mouse lymphoma, CHO chromosome aberration, human lymphocyte chromosome aberration, SHE cell transformation, rat and hamster bone marrow cytogenetics, and mouse dominant lethal test. Daily oral administration of imiquimod to rats, at doses up to 8 times the recommended human dose on a mg/m^2 basis throughout mating, gestation, parturition and lactation, demonstrated no impairment of reproduction.

Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women.

Imiquimod was not found to be teratogenic in rat or rabbit teratology studies. In rats at a high maternally toxic dose (28 times human dose on a mg/m^2 basis), reduced pup weights and delayed ossification were observed. In developmental studies with offspring of pregnant rats treated with imiquimod (8 times human dose), no adverse effects were demonstrated.

Nursing Mothers

It is not known whether topically applied imiquimod is excreted in breast milk.

Pediatric Use

Safety and efficacy in patients below the age of 12 years have not been established.

ADVERSE REACTIONS

In controlled clinical trials, the most frequently reported adverse reactions were those of local skin and application site reactions; some patients also reported systemic reactions. These reactions were usually mild to moderate in intensity; however, severe reactions were reported with 3X/week application.

These reactions were more frequent and more intense with daily application than with 3X/week application. Overall, in the 3X/week application clinical studies, 1.2% (4/327) of the patients discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.

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3X/WEEK APPLICATION
WART SITE REACTION AS ASSESSED BY INVESTIGATOR

MILD/MODERATE **SEVERE**
FEMALES **MALES** **FEMALES** **MALES**

	5% Imiquimod N=114	Vehicle N=99	5% Imiquimod N=156	Vehicle N=157	5% Imi qui mo d N= 114	Vehicl e N=99	5% Imiquim od N=156	Vehic le N=15 7
Erythema	61%	21%	54%	22%	4%	0%	4%	0%
Erosion	30%	8%	29%	6%	1%	0%	1%	0%
Excoriatio n/ Flaking	18%	8%	25%	8%	0%	0%	1%	0%
Edema	17%	5%	12%	1%	1%	0%	0%	0%
Induration	5%	2%	7%	2%	0%	0%	0%	0%
Ulceration	5%	1%	4%	1%	3%	0%	0%	0%
Scabbing	4%	0%	13%	3%	0%	0%	0%	0%
Vesicles	3%	0%	2%	0%	0%	0%	0%	0%

Remote site skin reactions were also reported in female and male patients treated 3X/week with imiquimod 5% cream. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%).

Adverse events judged to be probably or possibly related to Aldara reported by more than 5% of patients are listed below; also included are soreness, influenza-like symptoms and myalgia.

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	3X/WEEK APPLICATION			
	<u>FEMALES</u>		<u>MALES</u>	
	5%		5%	
	Imiquimod	Vehicle	Imiquimod	Vehicle
	(n=117)	(n=103)	(n=156)	(n=158)
<u>APPLICATION SITE DISORDERS:</u>				
APPLICATION SITE REACTIONS				
Wart Site:				
Itching	32%	20%	22%	10%
Burning	26%	12%	9%	5%
Pain	8%	2%	2%	1%
Soreness	3%	0%	0%	1%
<u>FUNGAL INFECTION</u> ^a	11%	3%	2%	1%
<u>SYSTEMIC REACTIONS:</u>				
Headache	4%	3%	5%	2%
Influenza-like symptoms	3%	2%	1%	0%
Myalgia	1%	0%	1%	1%

^a: Incidences reported without regard to causality with Aldara.

Adverse events judged to be possibly or probably related to Aldara and reported by more than 1% of patients include: **Application Site Disorders: Wart Site Reactions** (burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness); **Remote Site Reactions** (bleeding, burning, itching, pain, tenderness, tinea cruris); **Body as a Whole:** fatigue, fever, influenza-like symptoms; **Central and Peripheral Nervous System Disorders:** headache; **Gastro-Intestinal System Disorders:** diarrhea; **Musculo-Skeletal System Disorders:** myalgia.

OVERDOSAGE

Overdosage of Aldara 5% cream in humans is unlikely due to minimal percutaneous absorption. Animal studies reveal a rabbit dermal lethal imiquimod dose of greater than 1600 mg/m². Persistent topical overdosing of Aldara 5% cream could result in severe local skin reactions. The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg was hypotension which resolved following oral or intravenous fluid administration.

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DOSAGE AND ADMINISTRATION

Aldara cream is to be applied 3 times per week, prior to normal sleeping hours, and left on the skin for 6-10 hours. Following the treatment period cream should be removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. Aldara treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks.

Local skin reactions (erythema) at the treatment site are common. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides. Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara therapy. Handwashing before and after cream application is recommended. Aldara 5% cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm²; use of excessive amounts of cream should be avoided. Patients should be instructed to apply Aldara cream to external genital/perianal warts. A thin layer is applied to the wart area and rubbed in until the cream is no longer visible. The application site is not to be occluded.

HOW SUPPLIED

Aldara (imiquimod) cream, 5%, is supplied in single-use packets which contain 250 mg of the cream.

Available as: box of 12 packets. NDC 0089-0610-12.

Store below 25°C (77°F). Avoid freezing.

Rx only.

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/s/

Jonathan Wilkin
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Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles

Neil Swanson, MD,^a William Abramovits, MD,^b Brian Berman, MD,^c James Kulp, BS,^d
Darrell S. Rigel, MD,^e and Sharon Levy, MD^d

Portland, Oregon; Dallas, Texas; Miami, Florida; Exton, Pennsylvania; and New York, New York

Background: The approved imiquimod 5% cream regimen for treating actinic keratoses requires a long treatment time and is limited to a small area of skin.

Objective: We sought to evaluate imiquimod 2.5% and 3.75% for short-course treatment of the full face or balding scalp.

Methods: In two identical studies, adults with 5 to 20 lesions were randomized to placebo, imiquimod 2.5%, or imiquimod 3.75% (1:1:1). Up to two packets (250 mg each) were applied per dose once daily for two 2-week treatment cycles, with a 2-week, no-treatment interval between cycles. Efficacy was assessed at 8 weeks posttreatment.

Results: A total of 479 patients were randomized to placebo, or imiquimod 2.5% or 3.75%. Complete and partial clearance ($\geq 75\%$ lesion reduction) rates were 6.3% and 22.6% for placebo, 30.6% and 48.1% for imiquimod 2.5%, and 35.6% and 59.4% for imiquimod 3.75%, respectively ($P < .001$ vs placebo, each; $P = .047$, 3.75% vs 2.5% for partial clearance). Median reductions from baseline in lesion counts were 25.0% for placebo, 71.8% for imiquimod 2.5%, and 81.8% for imiquimod 3.75% ($P < .001$, each active vs placebo; $P = .048$ 3.75% vs 2.5%). There were few treatment-related discontinuations. Patient rest period rates were 0% for placebo, 6.9% for imiquimod 2.5%, and 10.6% for imiquimod 3.75%.

Limitations: Local pharmacologic effects of imiquimod, including erythema, may have limited concealment of treatment assignment in some patients.

Conclusions: Both imiquimod 2.5% and 3.75% creams were more effective than placebo and were well tolerated when administered daily as a 2-week on/off/on regimen to treat actinic keratoses. (J Am Acad Dermatol 2010;62:582-90.)

Key words: actinic keratosis; clinical trial; dose optimization; imiquimod.

From the Department of Dermatology, Oregon Health and Science University^a; Department of Dermatology, Baylor University Medical Center and University of Texas Southwestern School of Medicine^b; Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami^c; Graceway Pharmaceuticals, Clinical Development, Exton^d; and Dermatology, New York University Medical School.^e

Funding sources: Graceway Pharmaceuticals LLC.

Disclosure: Dr Swanson was an investigator and consultant for Graceway, and has received compensation for services. Dr Abramovits was an investigator and speaker for Graceway and has received compensation for services. Dr Berman was an advisory board member and speaker for Graceway and has

received compensation for services. Mr Kulp and Dr Levy are employees of Graceway. Dr Rigel was a consultant, advisory board member, and investigator for Graceway and has received compensation for services.

Accepted for publication July 1, 2009.

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Actinic keratoses (AKs) are common cutaneous lesions associated with chronic ultraviolet radiation exposure. Because of the similar genetic and histologic features, AKs are considered by some as incipient squamous cell carcinomas.^{1,2} If left untreated, up to 25% of AKs spontaneously regress within a year.³ However, patients with multiple AKs typically have them for long periods of time; the 10-year risk for developing an invasive squamous cell carcinoma has been estimated to be 6.1% to 10% for a patient with 7.7 AKs.⁴ As it is not possible to determine which individual AK lesions will progress to invasive squamous cell carcinoma, treatment of AKs combined with routine surveillance is recommended, especially in patients with evidence of photodamaged skin.^{5,6}

Imiquimod is a toll-like receptor-7 agonist that has been shown to boost the cutaneous immune response.⁷ Originally approved in 1997 for the treatment of external anogenital warts, imiquimod 5% cream was subsequently approved in 2004 as a topical treatment for AKs. The approved dosing regimen was application of 250 mg of cream, 2X/wk for a full 16 weeks, to a 25-cm² area on the face or balding scalp.^{8,9} Subsequently, a treatment regimen of 3X/wk for 4 weeks followed by a 4-week "therapeutic" no-treatment interval, and then by a second 4-week treatment cycle was approved in Europe.¹⁰⁻¹²

Although patient compliance to the approved dosing regimens was good in the clinical studies, the long duration of dosing may be inconvenient for some patients and affect compliance. One way to shorten treatment duration is to increase the frequency of treatment. However, in a dose-response study evaluating imiquimod 5% cream, daily dosing was not well tolerated.¹³ Therefore, to evaluate an imiquimod product that could be applied daily for AK for a short duration, and to expand treatment area to the full face/scalp, lower concentrations were assessed. Two identical, randomized, multicenter, placebo-controlled studies were conducted to evaluate the safety and efficacy of two new formulations of imiquimod cream, 2.5% and 3.75%. The creams were applied once daily to the entire face or balding scalp for two 2-week treatment cycles, separated by a 2-week, no-treatment interval. The results of a pair of

identical studies evaluating two 3-week treatment cycles are reported in an accompanying article.¹⁴

METHODS

Study population

Adults in general good health with 5 to 20 visible or palpable AKs, as determined by clinical assessment by the investigator, in an area greater than 25 cm² on

either the face or the balding scalp, but not both, were eligible for participation in the studies. A study patient could not have any significant condition in the treatment area that might impair evaluation, have atypical AKs (eg, AK > 1 cm²), be pregnant or lactating, have a chemical or alcohol dependency, or have an allergy to imiquimod or study cream excipients. Earlier therapy exclusions included: within 1 year before treatment initiation—imiquimod 5% cream on the head; within 90 days—interferon, interferon inducers, cytotoxic drugs, immunomodulators,

immunosuppressants, oral or parenteral corticosteroids, topical corticosteroids greater than 2 g/d, investigational drug or device use outside of the treatment area, dermatologic procedures or surgeries in the treatment area, and any AK therapy in the target treatment area; and within 30 days—imiquimod outside of the head, and topical prescription drugs and investigational drug or device use within treatment area. Use of any of the aforementioned treatments was also excluded throughout the study.

The studies were conducted in compliance with the Code of Federal Regulations of the US Food and Drug Administration (21 Code of Federal Regulations Parts 50 and 56), and International Conference on Harmonization Guideline E6 (Good Clinical Practice). The study protocols and informed consents were reviewed and approved by a central institutional review board or at specific institutions when required. All patients provided written informed consent before any study procedures. Enrollment for both studies began in January 2008, and all study procedures were completed by June 2008. The studies were registered on Clinicaltrials.gov on January 16, 2008, registration identifier NCT00605176.

Study design and study cream dosing

Patients were enrolled at 25 study centers in the United States in two identical designed studies

CAPSULE SUMMARY

- Short-course daily therapy with imiquimod 2.5% and 3.75% creams were both more efficacious than placebo cream in clearing actinic keratoses.
- Both imiquimod creams were well tolerated when applied to the full face or scalp using a regimen of two 2-week cycles of daily dosing with a 2-week, no-treatment interval.
- Lesion reduction was greater with imiquimod 3.75% than imiquimod 2.5%.
- Investigator-assessed photodamage improved more with the imiquimod creams than placebo cream.

Abbreviations used:

AE:	adverse event
AK:	actinic keratosis
ASR:	application site reaction
EOS:	end of study
IGIP:	Investigator Global Integrated Photodamage
LSR:	local skin reaction

conducted in parallel. Both studies included a screening phase, a treatment period (two 2-week treatment cycles separated by a 2-week, no-treatment interval), and a follow-up period (8 weeks) (Fig 1). Eligible patients were centrally randomized to placebo, imiquimod 2.5%, or imiquimod 3.75% cream in a 1:1:1 treatment allocation. Each study cream was identical in appearance to the others and contained the same excipients. The investigator selected the treatment area for each patient, either the entire face or the entire balding scalp, but not both. During each treatment cycle, patients applied up to two packets (250 mg cream/packet) of study cream once daily to the treatment area. Sufficient cream was applied as a thin layer to cover the entire treatment area, avoiding the periocular areas, lips, and nares, before normal sleeping hours and removed approximately 8 hours later with mild soap and water. Temporary dosing interruptions (rest periods) could be instituted by the investigator as needed to manage local skin reactions (LSRs) or adverse events (AEs). Treatment was resumed upon adequate resolution as determined by the investigator; however, doses missed because of rest periods or for other reasons were not made up and the duration of each dosing cycle remained at 2 weeks. After the baseline visit, patients were assessed at weeks 1, 2 (end of cycle 1), 4, 5, 6 (end of cycle 2), 10, and 14 (end of study [EOS]) (Fig 1). Patients who discontinued the study prematurely were requested to return for the EOS visit.

Efficacy evaluation

The primary efficacy parameter was the number of all visible or palpable AKs, baseline or new, in the treatment area as enumerated at each visit by the investigator. The primary efficacy end point was the complete clearance rate, defined as the proportion of patients at the EOS visit with a count of zero lesions in the treatment area. Secondary efficacy end points were the partial clearance rates, defined as the proportion of patients with 75% or more reduction in AK count in the treatment area at the EOS visit as compared with baseline, and the percent change in AK number at the EOS visit as compared with baseline. In addition, an Investigator Global

Integrated Photodamage (IGIP) score was assessed at the EOS visit. The IGIP score was an overall assessment of the patient's photodamage change from baseline in the treatment area (including an integrated assessment of fine wrinkling, coarse wrinkling, mottled pigmentation, roughness, sallowness, skin laxity and telangiectasias). The scoring was a 7-point symmetric scale ranging from significantly improved = +3 to significantly worse = -3.

Efficacy analyses were conducted on the combined intent-to-treat population composed of all enrolled patients from the two studies. For each of the studies, the sample sizes for each treatment group were selected to have 90% power to detect a difference in complete clearance rates of 30% for the active groups versus 5% for the placebo group. For the primary efficacy parameter, imputations were made for missing data points using last observation carried forward. All data from interim visits before the EOS or last visit (if lost to follow-up) were analyzed at their nominal time points. Complete clearance rates, partial clearance rates, and percent change in AK counts from baseline were analyzed using Cochran-Mantel-Haenszel statistics, stratifying by center. Confidence intervals were calculated using exact binomial statistics. For secondary efficacy variables of partial clearance and percent change in lesion number, each of the active arms and placebo were compared using the modified Bonferroni procedure of Hochberg.¹⁵

Safety evaluations

Safety was evaluated at each visit by measurement of vital signs, recording of AEs, and investigator assessment of LSRs. The LSRs were a defined set of local AEs (erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration) assessed independently of other AEs. At each visit, each LSR was graded as none, mild, moderate, or severe. At the prestudy visit and EOS visit, hematology, serum chemistry, and urinalyses were performed. For women of childbearing capacity, urine pregnancy tests were performed at prestudy, baseline, and EOS visits.

The AEs, including application site reactions (ASRs), were coded using the Medical Dictionary for Regulatory Activities (a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations), the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Treatment-emergent AEs were summarized for each treatment group by preferred term, intensity, and investigator assessment

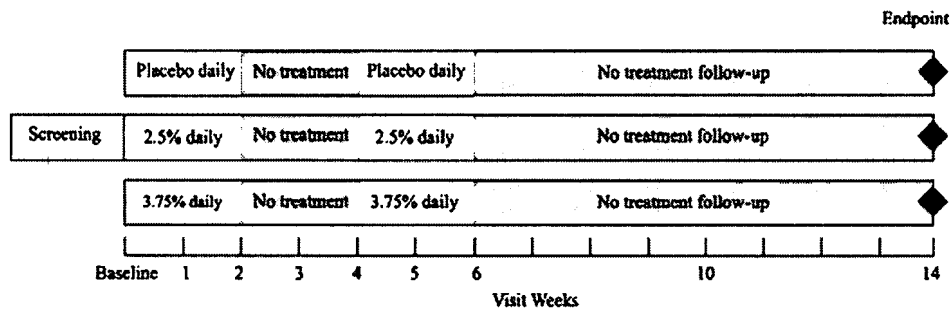


Fig 1. Study design. Each study was identical in design. Primary end point was assessed at end of study visit (week 14).

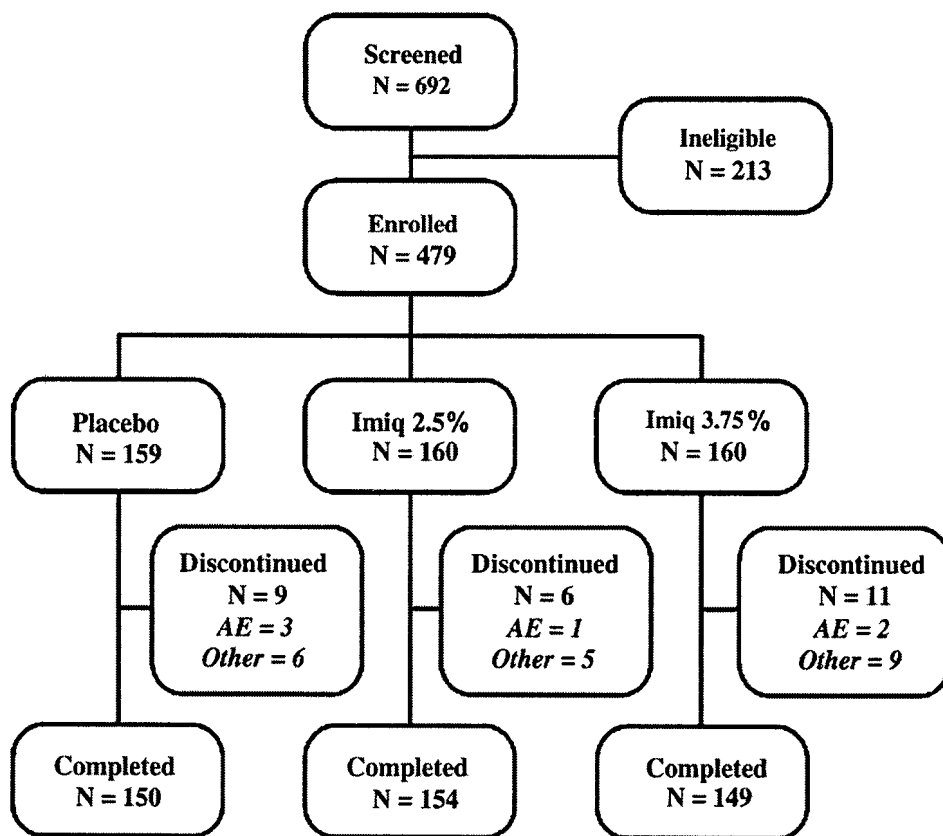


Fig 2. Patient disposition. AE, Adverse event; Imiq, imiquimod.

of relationship to study cream. Serious AEs and discontinuations because of AEs were summarized. The LSRs were summarized by the most intense score for each LSR and by the sum score at each visit and over the course of the study. All statistical analyses were performed using software (PC/SAS, Version 9.1.3, SAS Institute Inc, Cary, NC).

RESULTS

Patient population

In the combined studies, 479 male and female patients (Fig 2) were enrolled and 453 completed the

studies. The most frequent cause of discontinuation was personal reasons (10 patients), followed by AEs (6 patients). Overall, patients were predominantly male (>80%) and white (>99%), had a mean age of 64 years, and were predominantly treated on the face (>74%). The treatment groups were considered comparable with respect to demographic characteristics within and across the two studies (Table I). Overall, 96% of the patients were considered compliant with dosing per the study protocol, with greater than 95% compliance in each of the treatment groups.

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Table I. Patient characteristics by treatment group

Patients	Placebo 159	Imiquimod 2.5% 160	Imiquimod 3.75% 160
Age, y			
Mean (SD)	64.3 (8.9)	64.3 (10.5)	64.5 (10.6)
Median (range)	63.4 (43–89)	63.9 (40–90)	64.8 (36–90)
Sex, n (%)			
Male	130 (81.8)	127 (79.4)	132 (82.5)
Female	29 (18.2)	33 (20.6)	28 (17.5)
Race, n (%)			
White	158 (99.4)	160 (100)	160 (100)
Non-white	1 (0.6)	0	0
Ethnicity, n (%)			
Hispanic	5 (3.1)	4 (2.5)	6 (3.8)
Non-Hispanic	154 (96.9)	156 (97.5)	154 (96.3)
Fitzpatrick skin type, n (%)			
I or II	77 (48.4)	91 (56.9)	96 (60.0)
III-IV	79 (49.7)	65 (40.6)	63 (39.4)
V	3 (1.9)	4 (2.5)	1 (0.6)
Treatment location, n (%)			
Face	119 (74.8)	117 (73.1)	121 (75.6)
Balding scalp	40 (25.2)	43 (26.9)	39 (24.4)
Baseline AK, lesions			
Mean (SD)	11.3 (4.7)	10.9 (4.4)	11.0 (4.8)
Median (range)	10 (5–20)	10 (5–20)	10 (5–29)

AK, Actinic keratoses.

Efficacy

The overall median number of baseline AK lesions per patient was 10. Complete clearance rates, partial clearance rates, and percent reduction in AK lesions from baseline were all statistically significant for both imiquimod 2.5% and 3.75% compared with placebo overall (Fig 3). Efficacy for imiquimod 3.75% was numerically greater than that of imiquimod 2.5% for all of these outcomes, and statistically different at the EOS visit for both partial clearance ($P = .047$) and percent change in AK lesions from baseline ($P = .048$) (Fig 3). The median lesion counts transiently increased during both treatment cycles, and then decreased during the follow-up period for both imiquimod groups (Fig 4).

Within each study, both imiquimod 2.5% and 3.75% were superior to placebo with respect to complete clearance rates, partial clearance rates, and percent reduction in AK lesions from baseline. Complete clearance rates (and 95% confidence intervals) were 2.5% (0.3%-8.7%) and 10.1% (4.5%-19%) for placebo, 23.5% (14.8%-34.2%) and 38.0% (27.3%-49.6%) for imiquimod 2.5%, and 25.9% (16.8%-36.9%) and 45.6% (34.3%-57.2%) for imiquimod 3.75%, respectively, with P less than .001 for all pairwise active to placebo comparisons.

There was a greater increase in mean IGIP scores, and a greater proportion of patients who were

considered significantly or much improved, for both imiquimod groups compared with placebo group, and for imiquimod 3.75% compared with 2.5% (Table II). The improvements in IGIP scores were consistent with the clearance rate and lesion number results.

Safety

In the combined studies, no patient died, and there were 15 serious AEs reported in 12 patients (two placebo, 5 imiquimod 2.5%, 5 imiquimod 3.75%). Only one serious AE, severe diarrhea in a patient in the imiquimod 3.75% group, was considered by the investigator to be probably related to study cream. The AE was considered serious because of hospitalization for an elevated serum creatinine, subsequently determined to be a laboratory error, during evaluation of the diarrhea. No unexpected safety issues were observed. Six patients (3 placebo, one imiquimod 2.5%, two imiquimod 3.75%) reported 9 AEs that led to discontinuation from the study. Two patients discontinued because of AEs considered by the investigator to be related to study cream: one imiquimod 3.75% patient with headache, fatigue, pain, and application site pain, and one placebo patient with headache.

There was a greater incidence of patients in the imiquimod groups having any AEs and any

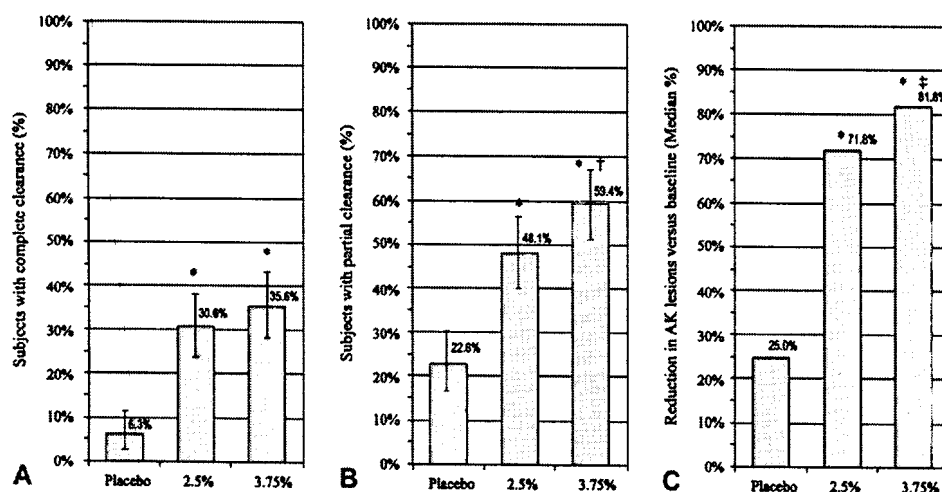


Fig 3. A, Complete clearance rates, with 95% confidence intervals (CI), by treatment groups for combined studies. * $P < .001$ for pairwise comparison vs placebo. B, Partial ($\geq 75\%$ reduction in actinic keratosis [AK] lesions compared with baseline) rates, with 95% CI, by treatment groups for combined studies. * $P < .001$ for pairwise comparison vs placebo. $^{\dagger}P = .047$ for pairwise comparison 3.75% vs 2.5%. C, Median percent reduction in AK lesions in treatment area compared with baseline by treatment group for combined studies. * $P < .001$ for pairwise comparison vs placebo. $^{\ddagger}P = .048$ for pairwise comparison 3.75% vs 2.5%.

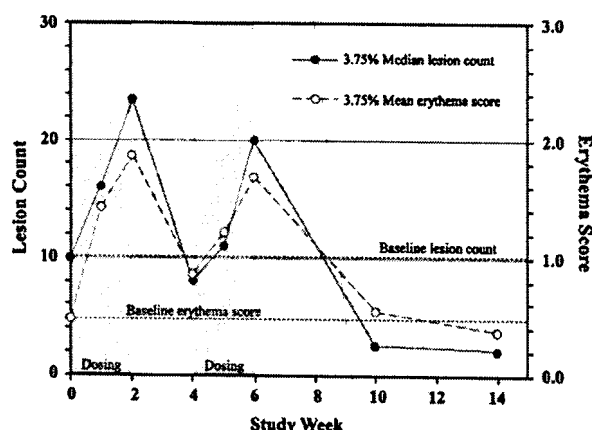


Fig 4. Change in lesion counts (median, left axis) vs change in erythema score (mean, right axis) for imiquimod 3.75% group by study week (similar profile for imiquimod 2.5% group). For patients with indeterminable lesion counts at visit, count was set above median for generating this display. Lesion count and erythema score at baseline are indicated by dotted lines. Dosing periods are indicated by shading. For erythema, 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

treatment-related AEs than in the placebo group (Table III). The AE terms reported by the most patients included headache, application site pruritus, fatigue, and nausea. As a group, ASRs were the treatment-related AEs reported by the most patients (Table III). There was a greater incidence of patients in the imiquimod groups requiring rest periods than in the placebo groups (Table III). Clinical laboratory values were generally within normal limits for all

parameters. Vital sign measurements and physical examinations did not reveal any significant safety concerns.

LSRs were observed in almost all of the patients during treatment. There was a greater incidence of patients experiencing LSRs, and severe LSRs, with increasing imiquimod concentration (Table IV). Erythema and scabbing/crusting were the LSRs observed in the most patients. The mean erythema score increased during each treatment cycle, and then decreased to below baseline during the follow-up period for both imiquimod groups (Fig 4).

DISCUSSION

The results of these two studies indicate that imiquimod 2.5% and 3.7% creams are effective in treating AKs on the full face or scalp in a short cyclical treatment regimen. For all efficacy outcomes, both imiquimod 2.5% and 3.75% were superior to placebo. In addition, imiquimod 3.75% was superior to 2.5% with respect to partial clearance rates and percent reductions in AKs lesions. Both imiquimod creams were well tolerated, with very few patients discontinuing from the study and more than 90% of patients complying with their assigned treatment schedules.

These studies examined the efficacy of imiquimod 2.5% and 3.75% creams to treat large areas of AK-involved skin, ie, the full face or bald scalp. Such a treatment field is consistent with clinical practice in which patients commonly present with AKs distributed across sun-exposed areas such as the face,

Table II. Investigator Global Integrated Photodamage score by treatment group

Patients with IGIP data	Placebo 151	Imiquimod 2.5% 153	Imiquimod 3.75% 151
Mean score (SD)	+0.73 (1.14)	+1.54 (1.21)	+1.94 (1.16)
Change status (numeric score)	n (%)	n (%)	n (%)
Significantly improved (+3)	14 (9.3)	43 (28.1)	64 (42.4)
Much improved (+2)	28 (18.5)	38 (24.8)	39 (25.8)
Slightly improved (+1)	24 (15.9)	35 (22.9)	28 (18.5)
No change (0)	73 (48.3)	34 (22.2)	17 (11.3)
Slightly worse (−1)	12 (7.9)	2 (1.3)	2 (1.3)
Much worse (−2)	0 (0.0)	0 (0.0)	0 (0.0)
Significantly worse (−3)	0 (0.0)	1 (0.7)	1 (0.7)

IGIP, Investigator Global Integrated Photodamage.

Table III. Summary of safety parameters by treatment group

Patients	Placebo 159	Imiquimod 2.5% 160	Imiquimod 3.75% 160
AEs, n (%)			
Any AE	53 (33.3)	70 (43.8)	77 (48.1)
Any treatment-related AE	4 (2.5)	19 (11.9)	31 (19.4)
Any severe grade AE	2 (1.3)	8 (5.0)	6 (3.8)
ASRs, n (%)			
Any ASR	2 (1.3)	10 (6.3)	17 (10.6)
>1 Patient for a group			
Application site pruritus	1 (0.6)	6 (3.8)	7 (4.4)
Application site irritation	0	4 (2.5)	5 (3.1)
Application site pain	0	2 (1.3)	5 (3.1)
Application site swelling	0	0	2 (1.3)
Rest periods, n (%)			
At least 1 rest period	0 (0.0)	11 (6.9)	17 (10.6)

AE, Adverse event; ASR, application site reaction.

scalp, or both. With the expansion of the treatment field from the 25-cm² area for the current imiquimod product, more AKs are likely to be treated during a single treatment course.

The complete clearance rate for imiquimod 3.75% cream observed in these studies was slightly lower than those previously reported for imiquimod 5% cream applied continuously for 16 weeks or as two 4-week cycles.^{8,10} However, those studies evaluated a smaller treatment area (25 cm²) with fewer baseline lesions (median 6). The lower clearance rate observed is not surprising; one would expect that with increasing baseline lesion number and treatment area, the probability of achieving complete clearance (zero baseline or new lesions in the treatment field) would decrease. Lesion reduction may be more appropriate to make comparisons across studies as it expresses gradations of response and normalizes for baseline disease severity. It may also be more applicable to clinical practice; a patient with a 90%

lesion reduction likely perceives clinical benefit, but would be considered a treatment failure using complete clearance as an end point. Although slightly more than a third of the patients treated with imiquimod 3.75% in these studies achieved complete clearance, the median lesion reduction was 82%. This degree of reduction is nearly identical to the median patient lesion reduction of 83% observed in the combined 16-week studies reported by Lebwohl et al.⁸

The field-based treatment approach used in these studies may account for the pronounced reductions in AKs, and for the improvements in investigator photodamage assessments. AK is considered a chronic, multifocal condition that occurs on a background of actinically damaged skin. In the photo-damaged skin around clinically apparent AKs, there are likely foci of abnormal keratinocytes present, some of which may subsequently manifest as AKs.^{16,17} These "subclinical lesions" would be

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Table IV. Incidence of local skin reaction of severe intensity by treatment group

	Placebo	Imiquimod	Imiquimod
Patients	159	2.5% 160	3.75% 160
Severe intensity			
Any LSR	2 (1.3)	33 (20.6)	54 (33.8)
Erythema, n (%)	0 (0.0)	23 (14.4)	40 (25.2)
Edema, n (%)	0 (0.0)	6 (3.8)	9 (5.7)
Weeping/ exudate, n (%)	0 (0.0)	2 (1.3)	9 (5.7)
Flaking/scaling/ dryness, n (%)	2 (1.3)	7 (4.4)	13 (8.2)
Scabbing/ crusting, n (%)	0 (0.0)	15 (9.4)	22 (13.8)
Erosion/ ulceration, n (%)	0 (0.0)	15 (9.4)	17 (10.7)

LSR, Local skin reactions.

subject to the same immune-mediated actions, initiated by imiquimod, to which clinically apparent AKs would be exposed. It was not surprising that, coincident with dosing, transient increases in lesion counts, up to a doubling, were observed in the imiquimod groups. This “unmasking” of subclinical lesions has been reported previously with imiquimod treatment.^{8,18} Of note, unlike some reports of other AK treatments in which the efficacy results were calculated only on clearance/nonclearance of AKs present at baseline, AKs present in the treatment field were counted irrespective of whether the lesions were noted at baseline or appeared de novo during the study.

Earlier studies in the treatment of AKs and superficial basal cell carcinoma indicated that tolerability of imiquimod 5% declines with increasing dosing frequency.^{8,18-21} In a dose-frequency response study of imiquimod 5% for AKs on the hands and arms, the proportion of patients with severe grade LSRs and those requiring temporary dosing interruptions (rest periods) increased with increasing application frequencies. Gebauer et al¹³ reported that greater than 30% of patients applying imiquimod 5% either 5×/wk or 7×/wk (daily) permanently discontinued treatment.

The current investigations demonstrate that daily applications with imiquimod 2.5% or 3.75% were both well tolerated when administered as two 2-week cycles separated by a 2-week, no-treatment interval, while also providing clinically relevant efficacy. Very few patients discontinued the study, and the highest incidence of rest periods was less than 11% (imiquimod 3.75% group). A dose response in side effects was discernible when comparing the imiquimod 3.75% group with the 2.5% group. In

earlier studies of imiquimod, ASRs were usually the most common spontaneously reported AEs. The incidences of any ASRs in the imiquimod 2.5% and 3.75% groups in this study, 6.3% and 10.6%, respectively, were relatively low compared with the 33% reported in the imiquimod 5% 16-week studies.⁸ This was somewhat surprising as it was expected that the more frequent dosing, larger treatment area, and greater baseline disease severity in the current studies would likely have increased local AEs. These appeared to have been offset by the reduction in imiquimod concentration, the short treatment cycles, and the incorporation of a built-in rest period (the no-treatment interval).

Erythema as an LSR was observed in most patients; about a quarter of patients in the imiquimod 3.75% group had severe erythema. However, no patients were sufficiently discomforted by the erythema as to require treatment discontinuation. The time course for the transient increase in both erythema intensity and lesion count corresponded closely to the days when drug was applied (Fig 4). Erythema has previously been identified as a pharmacodynamic effect of imiquimod, and these data are consistent with that response. This known and visible pharmacologic effect was a limitation of these studies as the concealment of treatment assignment may have been compromised in some patients. Although many patients had some degree of baseline erythema, the temporal increase in erythema intensity during dosing may have led to unblinding the investigators and patients. Although efficacy measures were obtained 8 weeks after completion of dosing, at a time when increases in erythema were likely resolved, investigators could have been biased in their efficacy assessments based on recall of earlier LSR assessments for a patient. Patient reporting of AEs as well may have been affected by assumptions on treatment assignment based on the presence of LSRs.

Another limitation of these studies is that AKs were evaluated by clinical assessment. Even among experienced dermatologists, there are diagnostic discrepancies in the clinical diagnosis of AK, as compared with histologic diagnosis.²² In addition, interobserver variation in the counting of AKs has been reported.²³ Biopsy of each lesion for histologic confirmation would have been impractical, however, and could have led to an interventional effect from the biopsies themselves. Furthermore, there may be interobserver variation in the histologic diagnosis of AKs by dermatopathologists.²⁴ Clinical diagnosis remains the standard for diagnosing AKs in clinical practice, and intracenter diagnostic and lesion counting bias should have affected each treatment group similarly, as the majority of

assessments at a study center were performed by the same investigator. Thus, despite the above limitations, the results observed in these multicenter studies should be generalizable to actual practice.

The results of two multicenter, double-blind, placebo-controlled studies demonstrate the efficacy and tolerability of imiquimod 3.75% and 2.5% creams applied daily in a two 2-week cycle regimen to treat AKs of the full face or scalp. With these new imiquimod formulations, AK treatment may be simplified and duration reduced for many patients. Further studies should evaluate these formulations for sustained clearance of AKs and for effectiveness in treating AKs on other body sites.

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