

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DERMATOLOGIC AND OPHTHALMIC DRUGS
ADVISORY COMMITTEE

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MEETING NO. 54

* * *

Thursday, November 16, 2000

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The Advisory Committee met in Conference Room 1066, 5630 Fishers Lane, Rockville, Maryland, at 10:00 a.m., in closed session, Dr. Robert Stern, Acting Chairman, presiding.

PRESENT:

ROBERT S. STERN, M.D., Acting Chair

ELIZABETH A. ABEL, M.D., Consultant

MICHAEL BIGBY, M.D., Guest

ROSELYN EPPS, M.D., Consultant

PRESENT (Continued):

HENRY W. LIM, M.D., Member

JOEL MINDEL, M.D., Ph.D., Consultant

EVA SIMMONS-O'BRIEN, M.D., Member

MING T. TANG, Ph.D., Consultant

JAIME HENRIQUEZ, Executive Secretary

C-O-N-T-E-N-T-S

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1 P-R-O-C-E-E-D-I-N-G-S

2 (10:02 a.m.)

3 ACTING CHAIRMAN STERN: Hello. I'm Robert
4 Stern, Acting Chair of the Dermatologic and
5 Ophthalmologic Drugs Advisory Committee. I'd like to
6 call Meeting No. 54 to order and welcome everyone.

7 This morning and this afternoon we'll be
8 discussing NDA 50-777 from Fujisawa Healthcare, a
9 product for the short and long-term treatment of signs
10 and symptoms of atopic dermatitis and pediatric
11 patients two years of age and older.

12 I'd like to begin with everyone around the
13 table introducing themselves.

14 DR. BIGBY: I'm Michael Bigby,
15 dermatologist from Boston.

16 DR. MINDEL: Joel Mindel, an
17 ophthalmologist and pharmacologist from Mount Sinai,
18 New York.

19 DR. SIMMONS-O'BRIEN: Eva Simmons-O'Brien,
20 dermatologist at Johns Hopkins University, School of
21 Medicine.

22 DR. TANG: Ming Tang, biostatistician, St.

1 Jude Children's Research Hospital, Memphis, Tennessee.

2 ACTING CHAIRMAN STERN: Robert Stern from
3 the Beth Israel Deaconess Medical Center in Boston, a
4 dermatologist.

5 MR. HENRIQUEZ: Jaime Henriquez from the
6 FDA.

7 DR. LIM: Henry Lim, dermatology, Henry
8 Ford Hospital, Detroit, Michigan.

9 DR. ABEL: Elizabeth Abel, clinical
10 professor of dermatology at Stanford, California, and
11 in private practice, Mountain View, California.

12 DR. EPPS: Roselyn Epps, pediatric
13 dermatology, head of Pediatric Dermatology, Children's
14 National Medical Center, Washington, D.C.

15 DR. BULL: Jonca Bull, Deputy Office
16 Director, Office of Drug Evaluation V in the Center
17 for Drug Evaluation and Research.

18 DR. WILKIN: Jonathan Wilkin, Director,
19 Division of Dermatologic and Dental Drug Products, ODE
20 V, CDER, FDA.

21 DR. OKUN: Marty Okun, clinical team
22 leader, Division of Dermatologic and Dental Drug

1 Products.

2 ACTING CHAIRMAN STERN: Thank you.

3 And now I'd like to ask Mr. Henriquez to
4 tell us about the conflict of interest statements.

5 MR. HENRIQUEZ: The following announcement
6 addresses the issue of conflict of interest with
7 regards to this meeting and is made part of the record
8 to preclude even the appearance of such at this
9 meeting.

10 Based on the submitted agenda and
11 information provided by the participants, the agency
12 has determined that all reported interest in firms
13 related by the Center of Drug Evaluation Research
14 present no potential for a conflict of interest at
15 this meeting, with the following exceptions.

16 In accordance with 18 USC 208(b), full
17 waivers have been granted to Dr. Joel Mindel and Dr.
18 Robert Stern. A copy of these waiver statements may
19 be obtained by submitting a written request to FDA's
20 Freedom of Information Office located in Room 12A-30
21 of the Parklawn Building.

22 In the event that the discussions involve

1 any other products or firms not already on the agenda
2 for which the FDA participants has a financial
3 interest, the participants are aware of the need to
4 exclude themselves from such involvement, and their
5 exclusion will be noted for the record.

6 With respect to all other participants, we
7 ask in the interest of fairness that they address any
8 current or previous financial involvements with any
9 firms whose products they may wish to comment upon.

10 Thank you.

11 ACTING CHAIRMAN STERN: Thank you.

12 And Dr. Wilkin will provide us now with an
13 overview of the issues of this meeting.

14 DR. WILKIN: Often the agency is very
15 interested in the Advisory Committee comments and
16 advice on significant new treatments, and this is a
17 new treatment. It's a new kind of modality. It's a
18 topical immune suppressant for atopic dermatitis.

19 The active agent is tacrolimus. The
20 sponsor is proposing two concentrations, a .03 percent
21 and a .1 percent, and the way we think about these
22 issues within the agency, we're actually presenting

1 the same paradigm to the committee. At the beginning,
2 we consider the question is there efficacy, and so the
3 first question: is there effectiveness of Protopic
4 0.3 percent, the lower concentration, in the treatment
5 of atopic dermatitis? In other words, is it superior
6 to its vehicle?

7 And then if the answer to that is yes, we
8 continue on with other questions. And the second
9 question is: is there sufficient evidence for
10 superior effectiveness of Protopic, 0.1 percent, the
11 higher concentration, compared to the 0.3 percent, in
12 adults and in children? And we would ask for those
13 answers separately.

14 The third question is: has the safety
15 profile of Protopic in the treatment of atopic
16 dermatitis been adequately determined for unrestricted
17 chronic therapy as a first line treatment in adults
18 for both concentrations, for children for both
19 concentrations?

20 And I would emphasize that this particular
21 question is not asking is it safe. It's asking has
22 the safety profile been adequately determined because

1 that's the question one asks before then you go on and
2 ask the question about safety.

3 And the question about safety is really
4 imbedded into the risk-benefit calculus in the fourth
5 question. The fourth question is: the proposed
6 indication for Protopic, which would allow for both
7 concentrations, for unrestricted chronic therapy, as
8 a first line treatment of atopic dermatitis in adults
9 and children two years and older, may be deconstructed
10 into the following elements, which may be
11 reconstructed into the indications.

12 And so what we've done for children two
13 years and up and for adults, if you could go through
14 and give us advice on what you think is appropriate,
15 unrestricted chronic versus time limited acute
16 therapy; first line versus second line treatment; the
17 lower concentration,; the higher concentration or both
18 or neither for a particular age subset; and then from
19 that we can reconstruct the indication and so we can
20 get to: is approval of Protopic recommended, and if
21 so, under what conditions, concentrations, first
22 versus second line, chronic versus time limited, acute

1 therapy, and in which age groups?

2 And then in the deliberation regarding all
3 of these different elements and the indication, you
4 may come up with items that you think some additional
5 studies would be helpful to inform labeling. So our
6 final question is: are there additional studies
7 needed to provide information important for the
8 labeling for Protopic? If so, what studies are
9 recommended?

10 And we've suggested some areas to think
11 about, but you're not limited to these. You could
12 come up with additional ones from what you hear today
13 and what you've read.

14 Consider the issues of lymphoma, local
15 suppression of immunity, photocarcinogenesis, and so
16 on.

17 Thank you.

18 ACTING CHAIRMAN STERN: Thank you.

19 I'd like to thank both the sponsor and the
20 FDA for providing us both with comprehensive materials
21 and also providing them in a very timely manner that
22 permitted us to review them other than in our hotel

1 room the night before the meeting, and that actually
2 has been very helpful at least to me.

3 And what I'd like to do next is take the
4 liberty of the chair and expand a little bit on my
5 perception of what the issues are, an overview of the
6 issues based on my reading of both the sponsor's and
7 the FDA's documents, where at least now I think the
8 issues are so that perhaps both the sponsor and the
9 agency can address those as we go along, and then, of
10 course, there will be time for questions and further
11 discussion after the presentations.

12 Could I have the first slide, please?

13 Well, as Jonathan has mentioned, I think
14 the issue here is really: is the .1 percent superior
15 to the .03 percent?

16 And in my reading of the data, the
17 significantly better outcomes were only in subgroup
18 analyses that were done post hoc, and in most of these
19 subgroup analyses, the magnitude of difference in
20 effect was small between the two, and many of these
21 significantly better outcomes were, in fact, no longer
22 significant after correction for multiple comparisons.

1 As I read -- next slide, please -- as I
2 read the data, one subgroup seemed to stand out with
3 significance even after appropriate correction for
4 multiple comparisons, which was those adults with the
5 greatest extent of disease and greatest severity, and
6 this led me to the reflection, is: could this be a
7 systemic effect due to the greater absorption with
8 resulting both direct cutaneous and also systemic
9 immune effects or much higher local levels accounting
10 for this difference in this subgroup?

11 And, of course, the question here is:
12 what are the safety implications of either greater
13 degrees of local or systemic immunosuppression as the
14 result of widespread use of the product in people with
15 greatest extent and severity of disease most likely to
16 absorb the product?

17 Next slide, please.

18 I had a few issues in terms of short-term
19 concerns. One is bacterial infections. We know that
20 people with atopic eczema often carry Staph. aureus,
21 and in fact, often develop impetigo. As I read the
22 data, it seemed that people with what were considered

1 to be active skin infections and recent antimicrobial
2 therapy were excluded from the trials.

3 Given this, I asked myself: what in a
4 more widespread community risk are the possible
5 effects both with respect to increase in infection and
6 spread of resistant strains from local Protopic use in
7 patients who might have Staph.

8 Next slide, please.

9 My other concerns or issues were what
10 about its effect on viral cutaneous illnesses, and
11 there was a difference reported between the frequency
12 of chicken pox VZV infections in the placebo and the
13 drug treated group, and I'd like to hear a little bit
14 more about that difference and how it was attributed
15 to an outbreak of chicken pox and how we can be sure
16 that's what was going on.

17 And I guess one thing, as much in my
18 anecdotal (phonetic), one thing that concerned me
19 was really rather little data with HSV or eczema
20 herpeticum addressing in the trial. Given that I've
21 never been an investigator and only practice one day
22 a week and in one patient who came to see me that

1 person was on an open label trial at another
2 institution in town and had classic beginnings of
3 eczema herpeticum near the eye and knew he was on
4 Protopic topically; so I'd like to hear a little bit
5 more about the HSV story in terms of frequency of
6 recurrences, spread, need for antiviral therapy, and
7 about that.

8 Next slide, please.

9 I think the longer term issues are really
10 long-term safety and lymphoma, as Dr. Wilkin has
11 mentioned. Because of my interest, I think, non-
12 melanoma skin cancer is an issue when you have
13 immunosuppression, and I'd like to talk about that for
14 a moment.

15 And as I understand it, there seems to be
16 a tendency towards perhaps recommending minimizing
17 exposure to sunlight while using the product, and one
18 has to ask: is that the kind of safety we need in
19 long-term use?

20 So next slide, please.

21 So I'd like to give my perspective on skin
22 cancer and immunosuppression. The first is: what

1 kinds of tumors are we concerned about there? What
2 length of exposure is significant? Is simultaneous
3 exposure to UV and the immunosuppressive therapy the
4 key issue? That is, is it order dependent? What is
5 the timing? And might younger patients be at
6 particularly high risk?

7 So in the next slide, in one slide this is
8 my perception about systemic immunosuppression in
9 transplant patients and skin cancer risk. Squamous
10 cell carcinoma risk is certainly increased. The risk
11 is greatest on sun exposed sites. It begins to
12 increase within a few years of therapy, and in fact,
13 even in low risk populations, such as people living in
14 Scandinavia, at tumor transplant doses, which are
15 mainly kidney, not heart or liver transplant doses,
16 within two years there are about 50-fold increases in
17 the risk of skin cancer, squamous cell carcinoma, and
18 beginning about five years, it's about a 100-fold
19 increase in risk. So very substantial increases.

20 Fortunately, I think even in people who
21 are undergoing systemic immunosuppression, melanoma
22 does not seem to be an issue, and if there are robust

1 data about the effect of long-term immunosuppression
2 on basal cell as aside from case reports, I wish
3 someone would tell me about them.

4 Next slide, please.

5 Well, we know that for the most part with
6 this agent in most patients we're talking about
7 cutaneous immunosuppression. So the question is:
8 what is the possible relevance of our experience with
9 systemic immunosuppression to an agent that appears to
10 in most cases have relatively little systemic, at
11 least non-regional systemic effects?

12 I think there's reasonable information
13 that immunosuppression limited to the skin may be
14 sufficient to increase skin cancer risk, and the
15 reason the evidence for this are a couple of things.

16 If you look at PUVA, Sorlens (phonetic),
17 and UVA, which are definitely immunosuppressive in the
18 skin, but not systemically by a whole variety of
19 experiments, squamous cell carcinoma began to occur
20 too quickly to be attributable only to the mutagenic
21 effects of the drug.

22 And, in fact, if you look at a nice

1 ordering experiment in people with CTCL, if you look
2 at the literature and you look at individuals who are
3 exposed to a very potent mutagen, topical nitrogen
4 mustard, for the treatment of this tumor and they have
5 PUVA afterwards, they often -- there's a number of
6 reports, quite persuasive, of the very rapid emergency
7 of many squamous cell carcinomas.

8 Whereas, if you do it in the other order,
9 you give them PUVA first and then the very potent
10 mutagen, very many fewer squamous cells emerge. So
11 cutaneous immunosuppression probably has a substantial
12 effect if mutagenesis has often occurred.

13 Next slide, please.

14 So I think what we think we know is that
15 it may be that long-term use of topical
16 immunosuppressive agents may increase squamous cell
17 carcinoma risk, and based on the evidence, I think it
18 may be that the greatest increase is in areas with the
19 greatest prior exposure or, in fact, perhaps
20 concomitant exposure to UV, the face, arms, hand,
21 upper chest, upper back, and one has to remember with
22 this product that in reading the materials, one of its

1 putative advantages over existing therapies, in fact,
2 the ability to use it on especially the face where the
3 alternative agents have undesirable long term effects.

4 Next slide, please.

5 Some things we do not know, which I think
6 are important and perhaps the sponsor can help us
7 with, is to what extent simultaneous UV and
8 immunosuppressive therapy the major risk factor for
9 increased skin cancer in immunosuppression and should
10 our greater concern be both the survival and
11 proliferation of greater numbers of UV mutated
12 keratinocytes due to immunosuppression and the
13 eventual or sooner development of tumors.

14 So this can be in either of two cases, one
15 with simultaneous exposure, basically mutated cells
16 that would have otherwise in some way been removed
17 from the epidermis and not had a chance in years hence
18 to go on to tumors surviving and going on at greater
19 frequency.

20 And the other is for already mutated
21 cells, will cutaneous immunosuppression have some of
22 them go on to tumors either in greater numbers or

1 sooner.

2 And so in conclusion, to me with perhaps
3 everyone always has their biases about what they think
4 about a lot of the time is I think it would be
5 important for us to address concerns about the -- on
6 the last slide. I'm sorry. No, that's it -- we must
7 be concerned that the long-term use of this agent
8 might increase skin cancer, and we have to be
9 concerned about that risk being especially great in
10 areas of the body where there's substantial past or
11 current exposure to UV for therapeutic agents used to
12 treat -- that are mutagenic -- that are used to treat
13 atopic dermatitis.

14 And we don't know whether we should be
15 more or less concerned about younger patients. I
16 think one always has to be more concerned about
17 potential agents that impact on cancer in young people
18 because they have a longer life expectancy for these
19 agents, that this increased risk could manifest
20 itself.

21 In addition, at least with UV there may be
22 some differences over development in terms of the

1 eventual carcinogenic risk of certain exposures
2 between young people and older people, even beyond
3 just more years at risk in a younger person.

4 With that, I'd like to ask the sponsor to
5 present, and the first presenter is Dr. Jerry Johnson.

6 DR. JOHNSON: Good morning. My name is
7 Jerry Johnson, and I'm the Vice President of
8 Regulatory Affairs, Quality and Safety at Fujisawa
9 Healthcare, and the sponsor of the tacrolimus ointment
10 NDA.

11 I would like to thank you, the Advisory
12 Committee, for your time and the opportunity to
13 present to you a summary of our information relating
14 to the use of tacrolimus ointment for the primary
15 treatment of the signs and symptoms of atopic
16 dermatitis in adults and children.

17 Previously, intravenous and oral
18 formulations of tacrolimus were developed by Fujisawa
19 Healthcare, Incorporated, and approved and marketed as
20 Prograf for the prevention of organ rejection in
21 transplant recipients.

22 Tacrolimus ointment is a topical

1 formulation of tacrolimus developed specifically for
2 the treatment of atopic dermatitis. Tacrolimus
3 ointment is the first in a new class of nonsteroidal
4 topical immunomodulators, and tacrolimus ointment,
5 Protopic, received marketing approval in Japan in June
6 of 1999.

7 In this worldwide development program,
8 more than 4,000 individuals have participated in 28
9 clinical trials, and data from this program were
10 presented in the tacrolimus ointment NDA and in your
11 briefing document that you've already read.

12 Our presentation today will focus on the
13 five core studies of that NDA which comprise the
14 primary support for the safety and effectiveness of
15 tacrolimus ointment.

16 In the United States, Fujisawa Healthcare
17 submitted the IND for tacrolimus ointment in December
18 of 1994. FHI, Fujisawa Healthcare, met with FDA at an
19 end of Phase II meeting in October 1996, and during
20 this meeting the pivotal clinical studies supporting
21 the NDA were agreed upon with the definition of the
22 primary endpoint.

1 A pre-NDA meeting was held in April of
2 1999, and FHI submitted the tacrolimus ointment, 0.3
3 percent and .1 percent, to the FDA on September 9th,
4 1999.

5 Atopic dermatitis is a chronic, life
6 altering disease affecting 15 million children and
7 adults in the United States and is characterized by
8 painfully red, swollen, itchy, flaky skin, and in some
9 cases the itching and redness is so vast and intense
10 that sufferers can scratch themselves to such an
11 extent that the risk of secondary infections
12 increases.

13 The visibility of eczema can lead to a low
14 self-esteem among these patients and the inability to
15 interact with others, especially in children and
16 teenagers.

17 Most atopic dermatitis cases are diagnosed
18 early in childhood. Many of these patients live with
19 their disease throughout their entire lives, and since
20 1970, the prevalence of atopic dermatitis has nearly
21 tripled.

22 For the past 40 years, corticosteroids

1 have been the mainstay of therapy for atopic
2 dermatitis. However, current treatment options are
3 limited, especially in children, and frequently
4 provide suboptimal control, particularly with long-
5 term use.

6 Our presentation today will show that
7 tacrolimus ointment fills a current therapeutic need
8 for a safe and effective, topical, nonsteroidal
9 ointment for the atopic dermatitis. Since this product
10 is effective monotherapy, it has an excellent safety
11 profile for use after one year and can be safely used
12 in children, even children as young as two years of
13 age.

14 Our presentation today will include Dr.
15 William Fitzsimmons, Vice President, Drug Development
16 Project Management, who will present pharmacological
17 information most relevant to tacrolimus ointment,
18 followed by Dr. Ira Lawrence, Senior Vice President of
19 Research and Development, who will present our
20 clinical efficacy and safety data.

21 The formal presentations will be followed
22 by a question and answer session.

1 We also have with us today Dr. Donald
2 Forbes, Senior Executive Photobiologist at Argus Labs,
3 developer of the current standard mouse model for
4 photocarcinogenicity testing; Dr. Amy Paller, Chief,
5 Division of Pediatric Dermatology and professor of
6 pediatrics of Northwestern University Medical School
7 who participated in two of the pediatric trials that
8 will be discussed today; and Dr. Lode Swinnen,
9 professor of medicine, Division of Hematology/Oncology
10 of Loyola University Medical Center.

11 Fujisawa is very proud of this development
12 program. We are excited that tacrolimus ointment will
13 provide the first new treatment option in several
14 decades for this chronic, life altering disease.

15 The FDA has posed several questions to you
16 today. These are somewhat paraphrased, but is
17 Protopic, .03 percent, effective in the treatment of
18 atopic dermatitis?

19 Is the .1 percent concentration more
20 effective than the .03 percent concentration in
21 adults, in children?

22 Is Protopic safe for unrestricted chronic

1 therapy as a first line treatment in adults for both
2 concentrations? In children, for both concentrations?

3 Is the approval of Protopic recommended,
4 and if so, under what conditions and for which age
5 groups?

6 And are there additional studies needed
7 for the labeling of Protopic, and what are they?

8 We believe that our presentation will
9 satisfactorily address all of these questions.

10 Dr. Fitzsimmons will begin our
11 presentation with a summary of the pharmacology and
12 toxicology of tacrolimus ointment. He will briefly
13 summarize the mechanism of action of tacrolimus,
14 followed by a presentation of the nonclinical data and
15 their relevance to the clinical situation with regard
16 to the hypothetical potential for events associated
17 with the systemic administration of tacrolimus.

18 His presentation will then move to
19 clinical pharmacology, focusing on a topic of
20 particular interest with this drug, namely, blood
21 concentrations following topical application.

22 Thank you.

1 Dr. Fitzsimmons.

2 DR. FITZSIMMONS: Thank you, Dr. Johnson.

3 Good morning. Tacrolimus ointment was
4 developed specifically for the treatment of atopic
5 dermatitis. Atopic dermatitis is a T cell mediated
6 disorder involving a dysregulation of IgE.

7 Tacrolimus acts directly on T lymphocytes,
8 especially CD-4 positive cells, by inhibiting
9 calcineurin. Calcineurin plays an essential role in
10 the intracellular signal transduction pathway leading
11 to the transcriptional activation of genes that encode
12 for the cytokines associated with atopic dermatitis.

13 Additionally, tacrolimus decreases the
14 inflammatory mediator release from skin mast cells and
15 basophils.

16 As you know, nonclinical studies are an
17 integral part of drug development. In this context,
18 tacrolimus ointment was evaluated in an extensive and
19 comprehensive topical pharmacology and toxicity
20 program in several animal species.

21 The program was conducted over a wide dose
22 range and included durations of application extending

1 from acute to lifetime exposure. Of the 27 studies
2 conducted, there are three studies that were chronic
3 and by that fact warrant some attention. These
4 include a 104-week topical carcinogenicity study in
5 B6C3F1 mice, a 52-week photocarcinogenicity study in
6 hairless mice, and a 52-week topical toxicity study in
7 micropigs.

8 In the topical carcinogenicity study, male
9 and female B6C2F1 mice were treated for at least 104
10 weeks, 24 months, essentially over the lifetime of the
11 animal. There was no increase in skin tumors observed
12 with tacrolimus treatment. Tacrolimus ointment does
13 not have a potential to induce skin tumors in this
14 model.

15 The systemic exposure to tacrolimus blood
16 levels in these mice was high, 89 times higher than
17 one would typically observe in patients with moderate
18 to severe atopic dermatitis.

19 This is not unexpected since it is known
20 that rodents have a much more permeable skin than man,
21 as well as other animal species.

22 One consequence of the high blood levels

1 in these mice was an increased incidence of non-
2 cutaneous lymphomas at the 0.1 percent concentration.
3 These lymphomas were not concentrated at the
4 application site. The increased rate of lymphomas is
5 clearly caused by the high skin permeability and
6 subsequent high blood levels in mice over prolonged
7 periods of time, resulting in systemic
8 immunosuppression.

9 This is different than humans where the
10 skin permeability is dramatically less, and blood
11 levels of this magnitude and systemic
12 immunosuppression are not seen.

13 A 52-week photocarcinogenicity study in
14 hairless mice is now routinely used in the development
15 program of all topical drug products. Please note
16 that this model requires that all animals in all dose
17 groups develop skin tumors. The primary metric is the
18 median time to tumor onset relative to the control.

19 As you can see in this slide, the median
20 time to tumor onset is decreased from 42 weeks in the
21 control group to a range of 34 to 35 weeks in the
22 vehicle .03 and .1 percent groups. For the 0.3 and

1 one percent groups, a further reduction in the onset
2 time to 31 weeks is seen.

3 Also, the tumor amplification factor is
4 increased to 1.3 in the vehicle .03 and .1 percent
5 groups and 1.5 in the .3 and one percent groups.

6 Although providing a consistent approach
7 to evaluate the photocarcinogenic potential, this
8 model is still undeveloped as to the relevance of the
9 findings to humans.

10 Several currently marketed topical
11 products have produced a reduction in time to tumor
12 onset in this model. Similar to these products, we
13 recommend that patients applying tacrolimus ointment
14 minimize or avoid exposure to natural or artificial
15 sunlight and use appropriate protective measures, for
16 example, sunscreens and protective clothing.

17 The 52-week topical toxicity study in
18 micropigs specifically investigated changes, both
19 topical and systemic, in an animal species that
20 allowed a juvenile to adult evaluation. The skin of
21 the micropig is considered to be the closest to that
22 of humans in terms of permeability and topical

1 response.

2 Absorption following topical application
3 based on AUC and blood concentrations is similar to
4 humans, less than one percent.

5 In addition, the blood levels following
6 topical application of 0.1 percent tacrolimus ointment
7 are similar to those documented in human patients.
8 Therefore, in contrast to the mouse studies, the
9 micropig allows assessment of the dermal and systemic
10 toxicity of tacrolimus ointment with absorption and
11 blood levels similar to atopic dermatitis patients.

12 In this large animal model, there were no
13 noteworthy topical or systemic findings attributable
14 to tacrolimus.

15 To summarize the nonclinical findings,
16 first, it has been established that tacrolimus is
17 neither a mutagen nor a carcinogen. Consistent with
18 this, the dermal oncogenicity study has shown on
19 increase in the incidence of skin tumors.

20 In mice with prolonged exposure to high
21 tacrolimus blood levels, immunosuppression results in
22 increased risk of lymphoma.

1 In a mouse model of photocarcinogenicity,
2 tacrolimus vehicle .03 and .1 percent concentrations
3 shortened the time to tumor onset by a similar amount.
4 Although the clinical relevance is unknown,
5 appropriate protection from the sun is warranted.

6 And in an animal model which closely
7 mimics the human situation, micropigs, there are no
8 noteworthy topical or systemic effects attributable to
9 tacrolimus.

10 I would now like to move from animals to
11 humans and present clinical data on the pharmacology
12 of tacrolimus ointment. In six patch test studies in
13 health volunteers and two pharmacodynamic studies in
14 atopic dermatitis patients, tacrolimus ointment was
15 shown not to induce contact hypersensitivity,
16 phototoxicity, or photosensitization.

17 In addition, tacrolimus ointment does not
18 reduce collagen synthesis or skin thickness.

19 The results of pharmacokinetic and
20 clinical studies in which blood concentrations were
21 evaluated indicate that there is minimal absorption
22 into the systemic circulation following topical

1 application of tacrolimus ointment.

2 For example, a pharmacokinetic study was
3 conducted in 39 atopic dermatitis patients, 31 adults
4 and eight children between the ages of five and 11
5 years. Patient supplied .3 percent tacrolimus
6 ointment once daily on the days of pharmacokinetic
7 evaluation, days one and eight, and twice daily on
8 days two through seven.

9 Note that this concentration is three to
10 ten times that of the proposed commercial
11 concentration.

12 The protocol defined area of application
13 was 50 or 100 square centimeters in children and
14 ranged from 100 to 5,000 square centimeters in adults.

15 Absorption was minimal. Absolute
16 bioavailability of less than or equal to .5 percent
17 following topical application, and there was no
18 evidence of systemic accumulation.

19 This low level of absorption was supported
20 by data from our Phase II and III trials. In clinical
21 trials, blood was collected during the course of the
22 study for a determination of tacrolimus blood

1 concentrations at various times after application of
2 .03 or .1 percent tacrolimus ointment.

3 The next three slides show the frequency
4 of quantifiable blood concentrations in U.S. clinical
5 studies. This frequency distribution is based on the
6 highest individual concentration observed in any
7 individual patient any time during the treatment.

8 This first slide shows the frequency
9 distribution for the .03 percent concentration in our
10 Phase III studies where blood was collected at weeks
11 one, three, and 12. Note that 70 percent of the
12 adults and 88 percent of the children applying .03
13 percent tacrolimus ointment did not have quantifiable
14 levels. That is, the highest concentration observed
15 was below .5 nanograms per mL, the limit of
16 quantitation for the assay.

17 Only two adult patients, one percent, had
18 a level of five nanograms per mL or higher, and this
19 concentration was transient.

20 Expanding this analysis to highlight the
21 78 pediatric patients from our Phase II and III
22 studies who received the intended concentration for

1 pediatrics, .03 percent tacrolimus ointment, 87
2 percent had concentrations less than 0.5 nanograms per
3 mL. No pediatric patient had a concentration greater
4 than or equal to two nanograms per mL, and there was
5 only one patient who had a concentration higher than
6 one, which was 1.19 nanograms per mL.

7 This slide shows the frequency
8 distribution for the .1 percent concentration from our
9 Phase III trials. Fifty-nine percent of the adults
10 and 80 percent of the children applying .1 percent
11 tacrolimus ointment did not have quantifiable levels.
12 Note that only one adult patient, .5 percent, had a
13 level of five nanograms per mL or higher, and again,
14 this concentration was transient.

15 In all three U.S. Phase III trials for
16 patients applying either .03 or .1 percent tacrolimus
17 ointment, a total of only three adult patients, .7
18 percent, and no pediatric patients had a level of five
19 nanograms per mL or higher, and this concentration was
20 not experienced for a prolonged period but only a
21 single sampling time and in one blood sample, a total
22 of three samples out of 1,156 collected.

1 To put these concentrations into
2 perspective, transplant patients are maintained for
3 their lifetime on oral or intravenous doses of
4 tacrolimus which result in minimum or trough
5 concentrations ranging from five to 20 nanograms per
6 mL.

7 If we now shift from the frequency
8 distribution to mean concentration data, this slide
9 shows the mean tacrolimus blood concentration at
10 evaluation time points during the course of the 12-
11 week double blind and up to one year open label Phase
12 III studies. These studies form the core of our NDA
13 submission.

14 There was no indication of systemic
15 accumulation with use up to one year. Mean
16 concentrations were lower in pediatric patients
17 compared with adult patients, even at the 0.1 percent
18 concentration.

19 Additionally, mean blood concentrations
20 were below 0.5 nanograms per mL at all time points.
21 These mean concentrations are less than one-tenth the
22 lower bound of the target trough concentrations in

1 transplantations.

2 To supplement this analysis, we performed
3 a population pharmacokinetic study which included data
4 from our six U.S. Phase III trials during which blood
5 was collected over a treatment period of three to 12
6 weeks. This analysis allows one to model the average
7 blood concentration that would be seen in atopic
8 dermatitis patients.

9 For patients in these six studies, the
10 average percent body surface area affected was 43
11 percent. Based on this model, there was minimum
12 absorption, and the population average steady state
13 tacrolimus concentration was .25 nanograms per mL. If
14 you take this average concentration of .25 and
15 multiply by the 24 hours in a day, you can calculate
16 an area under the curve of six nanogram hours per mL.

17 Additionally, we ran this analysis using
18 only pediatric patients as young as two years. The
19 average concentration in pediatrics was .21 nanograms
20 per mL.

21 One can use the estimated AUC determined
22 in this population PK model as a measure of what would

1 be the typical systemic exposure to tacrolimus
2 following topical application in both adult and
3 pediatric patients with moderate to severe AD.

4 Additionally, there are data available
5 from two recently conducted European pharmacokinetic
6 studies in adult and pediatric atopic dermatitis
7 patients in which the effect of increasing body
8 surface area on blood concentrations was evaluated.

9 The highest mean AUC over 24 hours
10 observed in these two studies was 20 nanogram hours
11 per mL in a group of adult patients treating the
12 highest affected body surface area. The mean AUC in
13 pediatrics was lower than in adults.

14 These data can be used to create a
15 hypothetical worst case scenario by making three
16 assumptions: that atopic dermatitis lesions do not
17 heal; that the percentage of body surface area
18 affected does not decrease with treatment; and,
19 therefore, quantifiable blood concentrations are
20 observed over prolonged periods of time.

21 All of these assumptions are contrary to
22 clinical evidence. the typical case and hypothetical

1 worst case can be used to estimate relative
2 differences in blood concentrations when evaluating
3 the potential in atopic dermatitis patients for events
4 that have been associated with systemic administration
5 of tacrolimus.

6 In order to make this comparison, we
7 analyzed the cumulative AUC for blood level exposure
8 in an average transplant patient, a transplant
9 recipient developing a lymphoproliferative disorder,
10 and the mice who develop lymphoma in the dermal
11 oncogenicity study.

12 While orally or intravenously administered
13 tacrolimus is not a mutagen nor a carcinogen, post
14 transplant lymphoproliferative disorder or PTLD has
15 been observed in a small percentage of transplant
16 recipients, less than five percent. PTLD is
17 associated with intense and excessive
18 immunosuppression and has been reported for a variety
19 of regimens designed to prevent graft rejection.

20 On average, transplant patients develop
21 PTLD at 122 days post transplant. So we use this as
22 the duration of treatment in these models.

1 The cumulative exposure in each of these
2 groups is shown on this slide. For the average
3 transplant recipient receiving tacrolimus, the
4 cumulative systemic exposure to tacrolimus is 75-fold
5 greater than the typical AD patient, 39-fold greater
6 than the hypothetical worst case AD patient.

7 For transplant recipients who develop
8 lymphoproliferative disorder while receiving
9 tacrolimus, the systemic exposure is 108-fold greater
10 than the typical AD patient and 56-fold greater than
11 the worst case.

12 And for the mice in the dermal
13 oncogenicity study where lymphoma was observed, the
14 systemic exposure to tacrolimus is 89-fold greater
15 than the typical AD patient and 46-fold greater than
16 the hypothetical worst case AD patient.

17 To summarize, the clinical pharmacology of
18 tacrolimus ointment, we have found systemic exposure
19 to tacrolimus in atopic dermatitis patients, even in
20 the hypothetical worst case, is minimal, far less than
21 that observed in nonclinical studies or in transplant
22 patients.

1 For patients with detectable blood levels,
2 there is no evidence of accumulation over time, and
3 the levels are transient.

4 In our studies, pediatric patients have a
5 lower frequency of detectable blood levels than adults
6 and lower mean levels compared to adults, and there is
7 a large safety margin between blood levels in the
8 typical or even hypothetical worst case AD patient and
9 the levels seen in transplant patients or the mouse
10 studies.

11 Dr. Lawrence will now provide data
12 supporting tacrolimus ointment as an effective and
13 safe agent in the treatment of atopic dermatitis in
14 both adults and children.

15 Dr. Lawrence.

16 DR. LAWRENCE: Thank you, Bill.

17 Dr. Stern, Dr. Wilkin, thank you very
18 much for allowing us to present to you today.

19 As mentioned earlier by Dr. Johnson, my
20 presentation will focus on the five Phase III studies
21 which formed the core of our submission and are the
22 primary support for the safety and efficacy of

1 tacrolimus ointment.

2 There were three randomized, double blind,
3 vehicle controlled, 12-week studies, the 37 in
4 pediatric patients and the 35 and 36 in adults, and
5 two open label safety studies which involved the
6 application of tacrolimus ointment twice daily for
7 periods up to one year, the 25 conducted in the United
8 States in children and the FG-12 conducted in Europe
9 in adults.

10 The five core studies involved 1,554
11 patients with moderate to severe atopic dermatitis,
12 1,226 of whom applied tacrolimus ointment and 328 who
13 used vehicle. Of these, 491 patients applying
14 tacrolimus ointment were less than 16 years of age.
15 Two hundred and fifty-eight of these were children
16 less than six years of age.

17 In today's presentation, I will present
18 efficacy data from the three 12-week, randomized,
19 double blind studies and safety data from all five
20 studies.

21 In the three 12-week studies, patients
22 were randomized to apply either 0.03 or 0.1 percent

1 tacrolimus ointment or a vehicle as a thin layer twice
2 daily to areas of active disease.

3 In patients with clearing of atopic
4 dermatitis, treatment was to have continued for one
5 week after clearing.

6 Patients were evaluated at baseline,
7 during treatment at the end of week one, two, three,
8 six, nine, and 12, or at the end of treatment if it
9 occurred earlier, as well as two weeks post treatment.

10 As shown in this side, eligibility
11 criteria, washout requirements, and concomitant
12 therapy restrictions were specified in the protocol.

13 I'd now like to look at the results. In
14 the three double blind, 12-week studies, a total of
15 983 patients, over 300 per group, were dispensed study
16 medication and treated. More patients in the vehicle
17 group compared with tacrolimus treated patients
18 prematurely discontinued primarily due to lack of
19 efficacy or they discontinued due to an adverse event.

20 Administrative reasons leading to
21 discontinuation were similar across the treatment
22 groups and included loss to follow-up, treatment

1 noncompliance, and patient's refusal to continue in
2 the study.

3 In each study and for the overall combined
4 data, treatment groups were comparable with respect to
5 gender, race, age, percent BSA affected and severity
6 of disease at the start of the study.

7 Of particular note is a excellent
8 representation of African Americans and young children
9 under the age of seven.

10 Please note the substantial representation
11 of difficult to manage patients. Forty-one percent
12 had more than 50 percent of the total body surface
13 area affected at baseline. Fifty-eight percent had
14 severe atopic dermatitis. "Severe" is defined by
15 criteria published by Drs. Rajka and Langeland.

16 Eighty-six percent had lesions involving
17 the head or neck, including the face.

18 The protocols for these studies did not
19 restrict application area. Patients were able to
20 treat all affected areas whether they were on the
21 face, around the eyes, or in the intertriginous
22 regions.

1 I'd like to move to the efficacy results
2 for these pivotal trials. I'd like to begin with the
3 results for the primary efficacy variable for each of
4 the three vehicle controlled trials. Then using
5 combined data from all three double blind studies, I
6 will present the primary efficacy variable, followed
7 by a comparison of the efficacy of the two ointment
8 concentrations.

9 In the 12-week double blind studies, the
10 primary efficacy endpoint was incidence of success
11 obtained from the physician's global evaluation of
12 clinical response defined as a rating of cleared or
13 excellent improvement at the end of treatment.

14 This slide summarizes the analyses
15 performed for success. An overall significant test of
16 equal proportions among the three treatment groups
17 allowed us to perform pair wise comparisons, primarily
18 each concentration versions vehicle and secondary pair
19 wise comparison was also performed versus 0.1 percent
20 and 0.03 percent concentrations.

21 These analyses were performed for each
22 individual study, for data from the three studies

1 combined, and for various subsets of adult patients.
2 The population analyzed was intent to treat. All
3 randomized patients who were dispensed drug applied it
4 at least once.

5 The last observation carried forward
6 convention was utilized.

7 This slide summarizes the success results
8 for the three identically designed 12-week randomized,
9 double blind studies. The success for each
10 concentration was significantly higher than that in
11 vehicle in each study, the pediatric 37, the adult 35,
12 and the adult 36.

13 As you can see from this slide, tacrolimus
14 ointment patients had a four to fivefold higher
15 success rate than did vehicle treated patients.
16 Success results were consistent across all studies and
17 were very robust.

18 Given the consistency of these result and
19 the identical design, we combined the data from all
20 three of these studies. Looking at the combined
21 success rate greater than 90 percent improvement, we
22 see that both concentrations of tacrolimus ointment

1 have a significantly higher success than vehicle.

2 Our success criterion of at least 90
3 percent improvement in the physician's global
4 evaluation is very strict. As a clinician I feel that
5 moderate improvement represents a meaningful benefit
6 to the patient.

7 The next slide shows the percentage of
8 patients receiving 50 percent improvement or greater
9 for the three 12-week, double blind studies combined.
10 Similar to the result using the strict success
11 criterion, significantly more patients in either
12 tacrolimus ointment group showed at least 50 percent
13 improvement when compared with vehicle, sixty-six
14 percent in the 0.3 percent, and 75 percent in the 0.1
15 percent compared to 22 percent in vehicle.

16 Thus, about three times as many patients
17 in either tacrolimus ointment group compared with the
18 vehicle group showed at least moderate improvement.

19 Not only did tacrolimus ointment result in
20 significantly greater improvement than vehicle, but
21 improvement was apparent early in treatment, usually
22 by the end of the first week.

1 Both concentrations of tacrolimus ointment
2 were statistically significantly more effective than
3 vehicle, which was confirmed by our secondary
4 endpoints, the eczema area and severity index, or EASI
5 score, a score developed by John Hanifin; the percent
6 body surface area affected; physician's assessment of
7 individual signs of atopic dermatitis; and the
8 patient's assessment of pruritus.

9 In the next few slides, I'd like to
10 compare the 0.1 percent and 0.03 percent tacrolimus
11 ointment concentrations with respect to efficacy,
12 highlighting comparisons only between the two
13 concentrations and not discussing vehicle.

14 First, I'd like to look at the primary
15 endpoint of success, greater than 90 percent
16 improvement. In each individual study, the 0.1
17 percent concentration consistently produced a
18 numerically higher success than the 0.03 percent.

19 Success for the 0.1 percent concentration
20 was statistically significantly higher than that for
21 the 0.03 percent concentration when data from the
22 identically designed two adult studies were combined.

1 Ten percent more adult patients achieved success with
2 this higher concentration.

3 The greater therapeutic benefit of the 0.1
4 percent concentration compared with the 0.03 percent
5 concentration was particularly evident in adult
6 patients with severe atopic dermatitis at baseline, as
7 you can see in this slide.

8 Another primary determinant of disease
9 severity is the percentage of body surface area
10 affected. As shown here, as the percent body surface
11 area affected increases, the differences in success
12 between the two concentrations become larger, reaching
13 statistical significance for those adult patients with
14 greater than 75 percent BSA at baseline.

15 Success in the 0.1 percent tacrolimus
16 ointment concentration was statistically higher than
17 that of vehicle for adult females. The added benefit
18 of the 0.1 percent tacrolimus ointment concentration
19 was also observed in African American adults. The
20 greater therapeutic benefit of the 0.1 percent
21 tacrolimus ointment for adult patients was also seen
22 in secondary efficacy parameters.

1 So in summary, both concentrations of
2 tacrolimus ointment are more effective than vehicle
3 for all patients in all efficacy parameters measured.
4 The response is rapid, usually within one week, and in
5 adult patients, the 0.1 percent tacrolimus ointment
6 concentration is more effective than the 0.03 percent
7 concentration, especially in adults with severe
8 disease and/or extensive affected body surface area.

9 Data from the two open label studies
10 support the maintenance of efficacy for the periods of
11 up to one year.

12 I'd now like to focus on safety beginning
13 with the three 12-week, double blind studies comparing
14 adverse event profiles for each tacrolimus ointment
15 concentration with vehicle, as well as between the two
16 tacrolimus ointment concentrations, followed by
17 adverse events in the two open labeled safety studies
18 and hazard rates for the adverse events.

19 Safety was assessed in the five core
20 studies based on the adverse event reporting, as well
21 as clinical laboratory data. All adverse events were
22 coded using a standardized COSTART dictionary and are

1 presented regardless of their relationship to study
2 drug.

3 A total of 1,554 patients were included in
4 the safety analyses, 983 in the 12-week, double blind
5 studies, and 571 in our open label studies.

6 In the three 12-week double blind studies,
7 nearly three times as many patients in the vehicle
8 group compared with either tacrolimus ointment group
9 prematurely discontinued treatment primarily due to a
10 lack of efficacy, resulting in fewer treatment days
11 for the vehicle group when compared with the
12 tacrolimus ointment treatment groups.

13 To correct for that difference in
14 treatment days between each of the ointment treatment
15 groups and the vehicle group, and to present a more
16 relevant comparison of these adverse events, Kaplan-
17 Meier analyses that adjusted for treatment days were
18 performed. The adjusted incident rate represents the
19 expected incidence of a given adverse event over 12
20 weeks.

21 This slide summarizes the adjusted 12-week
22 incident rates for adverse events observed in the

1 three studies combined regardless of potential
2 relationship to study drug. A higher incidence of
3 adverse events in the tacrolimus ointment groups
4 compared with vehicle was generally restricted to
5 local irritation events.

6 Note that vehicle and the tacrolimus
7 ointment groups had similar incidence rates for
8 overall adverse events, non-application site adverse
9 events, and infections, this being a predefined
10 cluster of infectious events.

11 Of particular note, fewer tacrolimus
12 ointment treated patients discontinued due to an
13 adverse event when compared to vehicle treated
14 patients.

15 I'd next like to take a brief moment to
16 describe the graphic presentation that I will now use.
17 This slide illustrates the difference between two
18 treatments and a 95 percent confidence interval
19 surrounding the treatment difference. The circle is
20 the observed difference and the lines represent the
21 boundaries of this confidence interval.

22 If the active group and vehicle are

1 significantly different, the 95 percent confidence
2 interval for the treatment group, that is, active
3 minus vehicle, does not cross zero.

4 On the other hand, if there is no apparent
5 difference between active and vehicle, the confidence
6 interval will cross the zero line.

7 Here we see the 12-week adjusted incidence
8 rates for common adverse events. The incidence in the
9 0.03 percent tacrolimus ointment group minus vehicle
10 is shown in yellow. The treatment difference between
11 the .1 percent concentration and vehicle is shown in
12 white. Events are in decreasing order of incidence.

13 In most cases, the incidents of most
14 adverse events were comparable between vehicle and
15 either concentration of tacrolimus ointment. The
16 exceptions are the local irritation events, skin
17 burning and pruritus, in both concentrations and flu-
18 like symptoms and headache in the 0.1 percent
19 concentration group, and as noted in your briefing
20 document, the lower incidence events of acne,
21 dyspepsia and cyst in the 0.1 percent group and
22 myalgia in both groups.

1 These local irritation events were of
2 short duration and occurred early in treatment,
3 generally during the first few days of treatment
4 before the patient's skin condition had improved, and
5 they rarely resulted in discontinuation of therapy.

6 Here we see the decrease in prevalence of
7 skin burning over time. The median duration of this
8 sensation ranged from 15 minutes to one hour after
9 application.

10 Other local irritation events, such as
11 pruritus and erythema, show a similar pattern.

12 This slide shows the adjusted incident
13 rates for other adverse events of particular clinical
14 interest: infections, based on a predefined infection
15 cluster; flu-like symptoms; headache; fever; increased
16 cough; and pharyngitis.

17 Differences between vehicle and tacrolimus
18 ointment groups are small and do not reach statistical
19 significance except for flu-like symptoms and headache
20 in the 0.1 percent group.

21 This slide shows cutaneous events of
22 particular interest: skin infections, folliculitis,

1 herpes simplex, skin tingling, alcohol intolerance,
2 that is, patients who experience skin or facial
3 flushing or redness or a heat sensation after alcohol
4 ingestion, or hyperesthesia localized to the
5 application site.

6 The next two slides look specifically at
7 adverse events in children. Only skin burning and
8 pruritus in the 0.03 percent concentration shown in
9 yellow had a higher incidence when compared to
10 vehicle. In the 0.1 percent tacrolimus ointment group
11 show in white, no event had a greater adjusted 12-week
12 incident rate when compared to vehicle.

13 If we continue on the next slide, you will
14 note that the adjusted incident rate of sinusitis is
15 actually higher in the vehicle group when compared to
16 the 0.1 percent tacrolimus ointment group, hence the
17 negative treatment difference shown on the slide.

18 This slide shows the adjusted incidence of
19 events of particular clinical interest in our
20 children: infection based on the infection cluster,
21 flu-like symptoms, skin infection, sinusitis, herpes
22 simplex, and chicken pox.

1 The difference in incidence among
2 treatment groups for these events is small. The
3 children with chicken pox did have a normal clinical
4 course lasting from four to seven days, and all
5 recovered fully without any clinical sequelae.

6 A total of 215 young children were
7 evaluated, 143 applying tacrolimus ointment and 72
8 applying vehicle. These patients have an adverse
9 event profile similar to that of the overall patient
10 population.

11 No adverse event had a statistically
12 higher adjusted incidence in the 0.1 percent
13 tacrolimus ointment group when compared to vehicle.
14 Only chicken pox and pruritus had a statistically
15 higher adjusted incidence in the 0.03 percent
16 tacrolimus ointment group when compared to vehicle.

17 I'd now like to turn to a comparison of
18 the incidence of adverse events between the two
19 tacrolimus ointment concentrations in both adults and
20 children combined. This slide shows the adjusted
21 incidence of the 0.1 percent group minus that in the
22 0.03 percent group for common adverse events. These

1 events are listed in decreasing order of incidence.

2 For these common events and for events of
3 lower incidence not shown here, no event had a
4 statistically higher incidence in the 0.1 percent
5 group when compared with the 0.03 percent group.

6 In summary, the results of the three 12-
7 week, vehicle controlled, double blind studies
8 demonstrate the safety of tacrolimus ointment. There
9 were no apparently differences between tacrolimus
10 ointment groups and vehicle with respect to the
11 overall incidence of all adverse events, non-
12 application site events, or infections as defined in
13 a predefined cluster.

14 Adverse events that do occur at a higher
15 incidence than in the vehicle group are generally
16 local irritation events of short duration occurring
17 early in treatment. No adverse event had a
18 statistically significantly higher incidence rate in
19 the 0.1 percent tacrolimus ointment group compared
20 with that in the 0.03 percent group.

21 I'd like to turn now to the safety of
22 tacrolimus ointment for longer term use. These open

1 label studies involve the twice daily application of
2 .1 percent tacrolimus ointment for up to one year.
3 Patients applied ointment on average for 87 percent of
4 their time on study, with half of the patients
5 applying ointment for 97 percent of their days on the
6 study.

7 In these studies, the majority of patients
8 had about one-third of their body surface area
9 affected. About half of the patients had severe
10 disease at baseline, and the majority of these
11 patients had head and/or neck, including facial
12 involvement.

13 Of the patients included in the safety
14 analyses for the open label studies, 465 were in the
15 study for at least six months, and 248 for at least 12
16 months.

17 As we review safety data for these two
18 open label studies, please bear in mind that we are
19 looking at adverse events over a one-year period in
20 patients with a chronic inflammatory disease.

21 This slide summarizes the overall adverse
22 event incidence in the two open label studies

1 regardless of possible relationship to study drug.
2 The more common application site adverse events in
3 both open label studies were the sensation of skin
4 burning and pruritus. The incidence of skin infection
5 probably reflects the natural course of patients with
6 moderate to severe atopic dermatitis.

7 The more common non-application site
8 adverse events, regardless of relationship to study
9 drug, were flu-like symptoms, headache, fever, and
10 asthma in the children, and flu-like symptoms,
11 allergic reactions, infection and headache in the
12 adult study.

13 The adverse event profile observed in
14 these open label studies was consistent with that
15 expected from patients with atopic diathesis who are
16 being observed for periods of up to one year.

17 The incidence of non-application site
18 adverse events did not increase with increasing length
19 of exposure, that is, cumulative treatment days or
20 cumulative ointment use.

21 The results of both long-term, open label
22 studies support the safety of 0.1 percent tacrolimus

1 ointment when used for periods up to one year in
2 children and adults.

3 I'd now like to discuss the safety
4 analyses performed using data from all five core
5 studies which were presented in greater detail in your
6 briefing document. In order to explore the potential
7 relationship between drug exposure over time and the
8 incidence of adverse events, time to onset analyses
9 were performed using data from all five core studies,
10 from patients applying the 0.1 percent tacrolimus
11 ointment, a total of 898 patients.

12 Remember that only .1 percent was utilized
13 in the long-term studies.

14 The events analyzed were those of
15 particular clinical interest in this patient
16 population and do not include local irritation events
17 which have been demonstrated to occur early in
18 treatment. Patients treated with .1 percent
19 tacrolimus ointment in all five studies contributed to
20 the analyses from day one through day 89, but only
21 open label study patients were included from day 90
22 onward.

1 This slide shows the time to event
2 analyses results for the two most common non-
3 application site adverse events: flu-like symptoms
4 and headache, as well as some additional events of
5 particular clinical interest, folliculitis, herpes
6 simplex, and lymphadenopathy.

7 The hazard rate analyses demonstrate that
8 there was no increased risk to patients over time with
9 regard to these adverse events or other events which
10 we do not show here. The issue has been raised about
11 whether the small numerical increase in
12 lymphadenopathy observed over time, which is not
13 statistically significant, but may be of clinical
14 significance, especially in children.

15 There were 11 cases in children in the
16 five core studies, with an additional two cases in the
17 global development program. All of these cases, nine
18 of which were in young children, resolved without
19 interruption of treatment due to this event.

20 This slide shows the hazard rate for
21 lymphadenopathy in the pediatric open label study in
22 which children applied .1 percent tacrolimus ointment

1 for periods of up to one year. Note that the rate
2 fluctuates over time.

3 I think it's important to point out that
4 most of the events COSTART coded as lymphadenopathy or
5 lymphadenitis secondary to an inflammatory process,
6 such as tonsillitis or a concurrent skin infection.
7 The investigator's terms which were eventually coded
8 as lymphadenopathy includes small cervical
9 enlargement, palpable or shotty cervical lymph nodes,
10 infected lymph glands, et cetera. All of these were
11 short-lived enlargements and are not uncommon in
12 patients at atopic dermatitis, especially children.
13 They appear to represent little clinical concern since
14 none of these events were associated with an
15 unexplained profound weight loss, fever, night sweats,
16 or progressive generalized node enlargement which
17 might signal a significant pathology.

18 Of the 33 cases of lymphadenopathy
19 observed for the 4,205 patients treated with
20 tacrolimus ointment in our global development program,
21 an incidence, by the way, of about .8 percent. Only
22 one event named axillary lump could not be explained.

1 Therapy was not continued, however, for this patient,
2 and they did resolve spontaneously.

3 There have been no cases of
4 lymphoproliferative disease in children in the
5 tacrolimus ointment development program to date. Two
6 cases of lymphoma have been observed in the global
7 tacrolimus development program in adults.

8 A B cell lymphoma in a 68 year old
9 presented in the parotid and was diagnosed as low
10 grade follicular lymphoma of the type not generally
11 associated with immunosuppression. It is also
12 important to note that this mass was present at the
13 time of entry into the study.

14 And mycosis fungoides. This is a patient
15 who had eczematous dermatitis for seven years,
16 diagnosed initially as atopic dermatitis at the age of
17 51 with his initial presentation. This suggests that
18 this may well have been his initial presentation for
19 CTCL.

20 Both cases of lymphoma occurred in adult
21 patients. Both cases were considered by the managing
22 investigator to be unrelated to the treatment with

1 tacrolimus, and in both cases the patients responded
2 fully to treatment.

3 In all five core studies, standardized
4 hematology and chemistry parameters were evaluated in
5 all adult patients and 56 percent of children. No
6 trends in laboratory profiles suggestive of a safety
7 concern were observed in either the 12 week or the
8 open label studies.

9 As might be anticipated in patients with
10 atopic dermatitis, eosinophil counts, IgE, and LDH
11 were elevated in many patients at baseline and
12 remained so during the studies.

13 Based on the results of the five core
14 studies, the risks associated with the use of
15 tacrolimus ointment are minimal and do not increase
16 with use up to one year.

17 Adverse events are generally local
18 irritation events of short duration, usually occurring
19 early in treatment. In control trials, there were no
20 statistically significant differences between the
21 vehicle and tacrolimus ointment groups with respect to
22 overall incidence of non-application site adverse

1 events or events in the predefined infection cluster.

2 No trends in clinical laboratory profile
3 were observed.

4 The safety profile observed in the five
5 core studies is consistent with that observed in
6 support of global studies as were provided in the NDA.

7 The FDA has proposed several questions to
8 you today, and I would like to present our responses
9 to these questions, as well, since Dr. Wilkin was kind
10 enough to present them to us yesterday.

11 The first question, is Protopic, 0.03
12 percent, effective in the treatment of atopic
13 dermatitis? We believe yes. In the three, 12-week,
14 double blind, vehicle controlled trials involving over
15 300 patients in each study, 0.03 percent tacrolimus
16 ointment was significantly superior to vehicle.

17 Is Protopic, 0.1 percent, more effective
18 than Protopic, 0.03 percent, in adults? We again
19 believe yes. In the two double blind, vehicle
20 controlled studies involving 632 adults, 0.1 percent
21 tacrolimus ointment was significantly more effective,
22 particularly evident in patients with severe disease

1 and extensive body surface area involvement.

2 Is Protopic, 0.1 percent, more effective
3 than Protopic, 0.03 percent, in children? No. In our
4 pediatric trials involving 351 children, there was no
5 significant difference in efficacy between the two
6 concentrations.

7 Is Protopic safe for unrestricted chronic
8 therapy as a first line treatment in adults for both
9 concentrations? Yes. The safety of the 0.1 percent
10 concentration of tacrolimus ointment in adults has
11 been established for up to one year, and thus
12 established the safety concurrently for the lower
13 concentration of 0.03 percent.

14 Is Protopic safe for unrestricted chronic
15 therapy as first line treatment in children for both
16 concentrations? Again, we believe yes. The safety of
17 the 0.1 percent concentration of tacrolimus ointment
18 in children has been established for up to one year.
19 As for adults, we have also by inference established
20 the safety of the lower 0.03 percent concentration.

21 The next question responds to unrestricted
22 chronic therapy versus time limited acute therapy. We

1 believe that unrestricted chronic intermittent therapy
2 is the most appropriate use of this drug. We would
3 recommend, as conducted in our clinical trials, that
4 patients should treat each episode to clearing plus
5 seven days and then discontinue treatment.

6 First line therapy versus second line
7 treatment. We believe that first line therapy is
8 appropriate. Tacrolimus ointment represents the first
9 new topical treatment for atopic dermatitis in several
10 decades and offers significant benefits over
11 conventional treatments which have well known adverse
12 events. Physician and patient should have the option
13 of utilizing this important new agent as first line
14 therapy to treat this debilitating and very life
15 altering disease.

16 With respect to the concentrations, 0.03,
17 0.1, both or neither, the 0.03 percent tacrolimus
18 ointment achieved a maximal efficacy in children. The
19 0.1 percent tacrolimus ointment showed additional
20 therapeutic benefit only in adults and particularly
21 those with severe disease and extensive body surface
22 area involvement.

1 The safety of 0.1 percent tacrolimus
2 ointment has been established for up to one year.
3 Therefore, the data support the approval of the 0.03
4 percent concentration in children and both
5 concentrations in adults.

6 Are there additional studies needed for
7 the labeling of Protopic? And what are they? We
8 believe that the NDA data we have summarized here
9 today have clearly demonstrated the safety and
10 efficacy of tacrolimus ointment for the treatment of
11 the signs and symptoms of atopic dermatitis in adults
12 and children.

13 We also believe that the depth and breadth
14 of this information is sufficient to provide clear
15 labeling for this product.

16 However, with any approved drug, Phase IV
17 investigations after approval will provide further
18 useful information.

19 We would also like to make a few further
20 recommendations for the use of tacrolimus ointment.
21 Patients should minimize or avoid unprotected exposure
22 to natural or artificial sunlight during therapy.

1 The use of tacrolimus ointment has not
2 been shown to increase the risk of developing
3 lymphoma. However, to be prudent, patients who have
4 unexplained fever or unexplained lymphadenopathy, or
5 who have suspected or proven infection mononucleosis
6 should delay the start of tacrolimus ointment therapy
7 or interrupt therapy until these symptoms have
8 resolved.

9 We believe tacrolimus ointment represents
10 a novel, safe, and effective nonsteroidal topical
11 therapy for the management of atopic dermatitis.

12 Thank you very much for your attention.

13 We'd now like to answer questions, and Dr.
14 Fitzsimmons will join me at the podium.

15 ACTING CHAIRMAN STERN: Thank you very
16 much for a very clear, succinct presentation, and
17 especially all aspects of it, including your final
18 summary.

19 DR. LAWRENCE: Thank you very much.

20 ACTING CHAIRMAN STERN: Questions from the
21 committee?

22 DR. MINDEL: Was there any attempt to

1 correlate blood level with effectiveness therapy?

2 DR. LAWRENCE: Yes, and I will ask Dr.
3 Fitzsimmons, please.

4 DR. FITZSIMMONS: Yes. We performed an
5 analysis to evaluate the success rate, and if I could
6 have slide number 269, please.

7 In this analysis, we looked at patients
8 who had quantifiable levels versus those who did not
9 and compared their success rate on the primary
10 endpoint, and as you can see, for the overall
11 population there is no difference: 33 percent success
12 rate in those with a quantifiable level versus 36
13 percent in those without. And this is similar also
14 whether you look at subsets of moderate or severe.

15 DR. MINDEL: I'm not sure that's exactly
16 what I was asking. I was asking whether the level in
17 terms of as the level increased was there a difference
18 rather than sort of grouping, grouping together. Your
19 numbers seem to small to me to be able to do that.

20 DR. FITZSIMMONS: Yes. What we tended to
21 see is that patients when they start therapy have
22 their flare of atopic dermatitis. At that time is the

1 most frequent time where you see quantifiable levels.
2 As that flare subsides and the therapy is effective,
3 the skin barrier becomes more effective and there is
4 lower quantifiable levels. You tend to see early
5 levels in those few patients that have them, and then
6 they drop off quickly as the topic dermatitis
7 improves.

8 DR. LAWRENCE: And I think, Dr. Mindel,
9 the point you made is very important. One of the
10 difficulties with that particular analyses, there were
11 so few patients that has measurable levels that it's
12 very difficult to really draw any strong inference
13 with regard to the level and efficacy over time. At
14 least most of them were only a single event.

15 DR. LIM: A question about the slide 15 on
16 the light source, the photocarcinogenesis study. What
17 type light source was used for the mouse model study?

18 DR. FITZSIMMONS: This was a UVR light
19 source, and maybe I could ask Dr. Forbes to clarify
20 exactly how this was done. He had performed this,
21 developed this model.

22 DR. FORBES: Thank you.

1 The light source is a xenon arc, a long
2 arc solar simulator that includes both the ultraviolet
3 and the visible portion of the spectrum. I can give
4 you any more detail that you would like to have, but
5 I don't want to bore you with it.

6 DR. LIM: So it covers both UVB as well as
7 visible light?

8 DR. FORBES: Yes. The UVB and UVA in
9 approximately the proportion that one would see at
10 about 35 degrees north latitude in the summer.

11 DR. LIM: And could I have a follow-up
12 question?

13 ACTING CHAIRMAN STERN: Of course.

14 DR. LIM: On the photosensitization, you
15 mentioned there was no evidence of photosensitivity.
16 You mentioned specifically phototoxicity, but then you
17 also mentioned about photosensitization. Is that
18 photocontact allergy, the protocol that you used?

19 DR. LAWRENCE: Yes. I'm sorry. That
20 wasn't clear. Yes, that's photocontact allergy in the
21 protocol.

22 DR. LIM: Thank you.

1 ACTING CHAIRMAN STERN: Thank you.

2 Dr. Bigby.

3 DR. BIGBY: I actually have a couple of
4 questions. The first thing, I'd like to compliment
5 you on in your toxicity data showing rate differences
6 with 95 percent confidence intervals, and I was
7 curious to know why you didn't present the efficacy
8 data that way as well, comparing drug and placebo and
9 the two concentrations.

10 DR. LAWRENCE: I think it was just a
11 graphical presentation choice. I apologize for that.
12 I do.

13 DR. BIGBY: Yeah, because I think it would
14 be helpful because it would show not only the
15 magnitude of the differences, but the precision, and
16 I think it would be quite revealing to have that
17 available.

18 DR. LAWRENCE: Actually, I can. If I
19 could have slide 872, these are the differences based
20 on success rate.

21 I apologize. I'm guilty for that. I like
22 the graphics better.

1 But here you see the treatment differences
2 and success rate. I apologize. I don't have a
3 pointer, but at the top is the two adult trials, and
4 at the bottom are the pediatric trials, and you can
5 see the first line is the .03 percent concentration.

6 Oh, thank you very much.

7 This is the .03 percent concentration
8 here, and then the .1 percent concentration here in
9 these studies.

10 DR. BIGBY: Okay. So there's similar data
11 for the difference between .03 and .1?

12 DR. LAWRENCE: I'm not sure if we have
13 those data. Let me just see. If I we, I'll be happy
14 to show you.

15 We do not have those. I apologize.

16 DR. BIGBY: Okay. Another series of
17 question. What incidence of tacrolimus-associated
18 lymphoma would you find unacceptable?

19 DR. LAWRENCE: I think any tacrolimus-
20 associated lymphoma would be unacceptable to us. We
21 believe that this is an important issue, especially in
22 children, but I think the challenge for us will be to

1 definitely have a clear relationship between the
2 lymphoma and the tacrolimus, especially in some
3 patients who have been treated with other potentially
4 bothersome products, such as oral cyclosporin or other
5 oral immunosuppressive agents, as well as some light
6 therapies, as well, which we do know have
7 immunosuppressive agents, as well.

8 DR. BIGBY: So that means that if after
9 the drug is approved there's a case of tacrolimus-
10 associated lymphoma, you'd come back and say you
11 wanted to take it off the market?

12 DR. LAWRENCE: Well, I think, again, that
13 would be a difficult question to answer. I would say
14 that certainly we do not wish to have and do not
15 believe that there is a risk of lymphoma, based on our
16 current data. I don't think I'm prepared to make a
17 specific statement about what the level would be. I
18 think we'd certainly want to work with the agency on
19 something like that and develop guidelines.

20 I apologize for my misstatement earlier.

21 DR. BIGBY: So then the other part to that
22 question is, you know, based on your current

1 estimates, what's the upper 95 percent confidence
2 interval of your estimate of the risk of a patient
3 developing a lymphoma while using tacrolimus?

4 DR. LAWRENCE: Bill, would you like to
5 address that?

6 DR. FITZSIMMONS: Well, at this point the
7 incidence is zero. There are no cases in our total
8 database. So we have not calculated a confidence
9 interval around that zero. There is --

10 DR. BIGBY: But you can, you know. You
11 can based on the number of patients exposed and their
12 length of exposure.

13 DR. FITZSIMMONS: We just have not
14 calculated that confidence.

15 DR. BIGBY: Okay. Can I do a couple more?
16 How was African American defined in your
17 study?

18 DR. LAWRENCE: This was on the case report
19 forms. Patients were asked to be identified by the
20 managing physician as either Caucasian, Oriental,
21 African American, Latino or Hispanic or Other. So it
22 was left up actually to the individual managing

1 physician.

2 DR. BIGBY: Okay, and so given that, do
3 you have any biologic explanation for why one percent
4 was more effective or .1 percent was more effective
5 than .03 percent in patients who were self-defined as
6 African American?

7 DR. LAWRENCE: We actually have looked at
8 that. I am not aware of a strong biological reason.
9 There certainly is evidence in the clinical literature
10 that in some cases African American or other patients
11 of color do benefit from different strengths of drugs
12 or different concentrations of topically applied
13 drugs.

14 I'm afraid I don't have a very strong
15 reason for that observation other than to just say
16 that we did see it, and we noted it consistently in
17 the adults.

18 DR. BIGBY: Did you adjust for severity in
19 looking at differences between racial groups?

20 DR. LAWRENCE: We did adjust both for
21 severity and also other characteristics, such as
22 erythema, et cetera.

1 DR. BIGBY: And this is my last comment.

2 DR. LAWRENCE: That's okay. Please.

3 DR. BIGBY: You talked about combining the
4 results of studies. Was that just done by sort of
5 adding the total number of patients and sort of
6 recalculating it based on, you know, totals?

7 Because that's actually not a correct way
8 to combine studies.

9 DR. LAWRENCE: Perhaps the best thing for
10 that since I claim not to be a statistician is to as
11 Mr. Yoichi Satoi, who is the statistician to come up
12 and specifically address that question. I don't want
13 to misstate anything.

14 DR. SATOI: My name is Yoichi Satoi. I'm
15 a statistician.

16 Could I clarify in terms of efficacy
17 analysis or safety analysis?

18 DR. BIGBY: Efficacy.

19 DR. SATOI: Efficacy. Actually our
20 efficacy analysis combining studies based on
21 stratified analysis, study as a strata. So it means
22 study is taking into account of (unintelligible), not

1 just the overall crude analysis, but kind of a
2 combined study.

3 DR. BIGBY: So, you know, in meta analysis
4 when you combine studies, you either do it based on
5 random or fixed effects models. Is this what you did?

6 DR. SATOI: We used stratified analysis
7 using a Mantel-Haenszel type approach. So it means we
8 used study as a fixed effect.

9 DR. BIGBY: Thank you.

10 ACTING CHAIRMAN STERN: Dr. Epps.

11 DR. EPPS: Thank you.

12 I just have a brief question. There were
13 in your thorough booklets and in presentation -- thank
14 you very much for that -- there was a discussion of
15 herpes zoster infection, and five of the cases were
16 reported as chicken pox in kids. Was the immunization
17 status of all the kids -- were they all up to date
18 when they entered the study, and had these kids been
19 immunized?

20 DR. LAWRENCE: I apologize. I truly do
21 not know that.

22 DR. EPPS: Okay.

1 DR. LAWRENCE: We did not collect that
2 information with regard to immunization status. So I
3 really can't answer that. I apologize. Certainly we
4 can try and get that.

5 DR. EPPS: Well, I would be curious about
6 the ones who did present, who did evolve or had
7 chicken pox, whether or not they had been previously
8 immunized.

9 Thank you.

10 ACTING CHAIRMAN STERN: Other questions
11 from other committee members? Dr. Tang.

12 DR. TANG: Yeah, this is Ming Tang.

13 I have a question on the efficacy study.
14 So you have used, as I understand, you have used the
15 intend to treat analysis, and it is stated in slide 36
16 that 64 of the patients discontinued. So at the end of
17 12 weeks, how many patients were included in your
18 analysis?

19 DR. LAWRENCE: Well, all of the patients
20 were included. We did --

21 DR. TANG: So you were able to evaluate
22 them at 12 --

1 DR. LAWRENCE: Yes, we used a last value
2 carried forward. So if the patient left the study at
3 whatever week and they were counted as a failure, that
4 failure was carried forward. That was true of all
5 treatment groups, so that we did have a full number of
6 patients to evaluate from the efficacy standpoint.

7 ACTING CHAIRMAN STERN: Other questions
8 from committee members?

9 (No response.)

10 ACTING CHAIRMAN STERN: Then if it's all
11 right, I'd like to ask a few.

12 DR. LAWRENCE: Please.

13 ACTING CHAIRMAN STERN: I guess one is on
14 the .03 versus .1 percent in adults. I noted that
15 there was a difference in dropout rates, higher in the
16 .03 than the .1, and you appropriately used intention
17 to treat, but, in fact, I wonder if you used people --
18 and the reasons for drop seem to be quite independent
19 of the drug where there were differences -- I noted
20 you used intention to treat, and in fact, I wondered
21 what would happen to success rates if you only used
22 individuals who, in fact, completed therapy in the

1 final analysis.

2 That would tend to lower the difference in
3 the proportion of individuals improved between the .03
4 and .1, and since your P was only .04, it may have
5 made that a nonsignificant effect.

6 DR. LAWRENCE: I'm not sure if we have
7 those analyses done. I will wait till my crew
8 comes --

9 ACTING CHAIRMAN STERN: It's just that
10 when you're very close on making significance, I think
11 you have to look at other things that might have
12 affected your analysis, although you did the
13 appropriate one, and I think that's something to keep
14 in mind in the arguments.

15 DR. LAWRENCE: Thank you. That's a very
16 good point.

17 ACTING CHAIRMAN STERN: Sir, could you --
18 sure.

19 DR. FITZSIMMONS: If I could make one
20 clarification on that. Can you display slide 858?

21 If you look early on, before the end of
22 treatment, you can see that at each evaluation time

1 point in these studies and before many of the
2 discontinuations occur there is a continuous
3 difference between the yellow bar here, which is a
4 .03, and the .1, which tends to get greater over time.

5 That's not an analysis of only the
6 completers, but tends to show that even before
7 dropouts occur, that difference starts.

8 ACTING CHAIRMAN STERN: I have a number of
9 in a sense safety related questions, some of which are
10 informational. One is I noticed in the children, the
11 area of application was, I believe, 50 to 100 square
12 sonometers, and that when I did my math to bring it
13 back into the English system is essentially between a
14 three inch square and a five inch square, not a large
15 area of application, if I read that slide correctly.
16 Did I?

17 DR. LAWRENCE: Yes, that is correct just
18 for the 08 pharmacokinetic study.

19 ACTING CHAIRMAN STERN: I understand, but
20 in terms of the data where we're getting systemic
21 absorption, we're talking about areas no larger than
22 this. That's about 100 square sonometers.

1 What I'd be interested in is do you have
2 any data looking at the skin in terms of T cell
3 profiles, in terms of cytokines, in terms of what's
4 going on when, in fact, you treat an individual with
5 atopic dermatitis when both initially and when they're
6 cleared with this product systemically and topically?

7 DR. LAWRENCE: We do not have a comparison
8 between systemic and topical tacrolimus. We did
9 conduct a very small study that was actually presented
10 last year at the Society of Investigative Dermatology,
11 comparing some cytokine markers in the skin in
12 patients with atopic dermatitis looking at
13 triamcinolone versus tacrolimus, and in that study
14 there was obviously diminution in several cytokines.
15 A greater number of cytokines were actually diminished
16 with triamcinolone versus tacrolimus.

17 In all of those patients they were treated
18 for three weeks, measured at baseline, week three, and
19 then stopped, and then measured again at two weeks
20 post.

21 What we found was that the IL-13 was
22 diminished significantly in the tacrolimus treatment

1 arm and similarly also in the triamcinolone arms.
2 However, in the triamcinolone arm we also saw
3 decreases in other markers, including Langerhans cells
4 and macrophages, which we did not see that change in
5 the tacrolimus arm.

6 We don't have, unfortunately, Dr. Stern,
7 any comparison to systemic and topically.

8 ACTING CHAIRMAN STERN: I guess from a
9 safety point of view to me the most direct way, aside
10 from studies in humans, to approach this issue of at
11 least skin cancer is to really look at to what extent
12 are there changes that are measurable in the skin that
13 are comparable between the topical agent and where the
14 oral agent is used because I think many of us would
15 believe that much of what might go on with respect to
16 the promotion or permission of at least squamous cell
17 carcinoma is like to be events in the skin rather than
18 events that would be reflected in systemic levels.

19 And I guess the next question is really a
20 little bit extending on Michael's question. In terms
21 of lymphoma in transplant patients, I don't have a
22 good concept of -- I think I heard you say that two

1 years is the mean or median time of onset. Could you
2 educate us about age groups at risk and how long it
3 takes to manifest itself?

4 DR. FITZSIMMONS: Yes. In the transplant
5 setting, again, where they have chronic maintenance
6 immunosuppression with multiple agents, such as
7 tacrolimus, steroids, azathioprine or mycothenolate,
8 the incidence of PTLT is less than five percent. It
9 depends on the organ transplant that you look at.

10 The median time to onset in our tacrolimus
11 database, which is quite extensive, is 122 days post
12 transplant, and the risk factors, the main risk
13 factors relate to the age of the patient, with
14 pediatric patients being at higher risk based on their
15 EBV serology than adult patients. But these tend to
16 be early events, usually within the first year post
17 transplant.

18 ACTING CHAIRMAN STERN: Have you looked at
19 your data to see if there's any relationship between
20 mean or median time to the event and dosage of the
21 drug or, for example, comparing livers, kidneys and
22 hearts, where there tend to be very different

1 maintenance levels of doses?

2 DR. FITZSIMMONS: There is a relationship
3 between the blood concentration of tacrolimus and the
4 risk of post transplant lymphoproliferative disease in
5 these patients, and that's across kidney, liver, and
6 the solid organs.

7 ACTING CHAIRMAN STERN: But my question
8 was sort of an extension on that. If you take people
9 who have lower systemic levels, do they have a longer
10 mean time?

11 What I'm sort of asking is: do we know if
12 there's really a threshold here, and may it be a
13 product of concentration times time that's important?

14 DR. FITZSIMMONS: The main factor in that
15 onset time is actually the primary EBV infection,
16 which oftentimes occurs because of the organ that's
17 transplanted being EBV positive or the blood products
18 that are given. So that the time onset is really
19 related to the EBV, not necessarily to the duration of
20 the systemic immunosuppression.

21 ACTING CHAIRMAN STERN: Thank you.

22 One issue, I think, for all of the safety

1 things is you have -- and this is both a comment and
2 a question -- you have a one-year database. My
3 understanding is that these individuals use this drug
4 on an as needed basis. So, in fact, the total time of
5 exposure in most cases is likely to be substantially
6 less than 365 days.

7 My first question is: what were the
8 quantities used? I assume in all of these trials,
9 especially the long-term ones, you had people bring
10 back the tubes, and you have some idea of how much was
11 applied. Could you give us some idea of the range of
12 amounts of product, the mean?

13 DR. LAWRENCE: I'll get away from my
14 slides to come up here, but, yes, we have, indeed,
15 collected those data in both the short-term and long-
16 term studies.

17 While we're waiting for those data, it's
18 also important, Dr. Stern, that in the long-term
19 studies, the average number of days on study was
20 actually about 270 days. So many patients chose to
21 continue on the drug even though they had to have some
22 lesions clear.

1 Also, frequently what we see is that
2 patients will clear in one area and they'll have a
3 breakthrough in the other, and they'll just continue
4 to apply. Actually the mean number of treatment days
5 in the long-term pediatric study was 279, if my memory
6 serves me pretty well.

7 If I could have slide 298, please, this
8 addresses your question, Dr. Stern, and I'm going to
9 have to put glasses on. I apologize.

10 ACTING CHAIRMAN STERN: Yeah. I'm having
11 trouble, too.

12 DR. LAWRENCE: You see here, again, the
13 number of treatment days, and these are the pediatric
14 and adult 12-week trials first off. So these are only
15 12 weeks, which should give you a little idea. I'm
16 sorry, yeah.

17 The total grams used was about the same in
18 the vehicle, the 0.03 and the 0.1 percent group, in
19 pediatric patients, around 280 to 300 grams.

20 The adults, as you can imagine, had a
21 higher number of grams used. This is primarily, I
22 think, because they just stopped, and when we

1 calculate the total amount used, they certainly had a
2 larger body surface area and used it for shorter
3 periods.

4 If you look at the average daily ointment
5 use in grams, you can see interestingly that actually
6 the vehicle patients used more. I don't know if they
7 were trying to add more for benefit or not, but
8 certainly about, on average, about four grams in the
9 children and about six grams in the adult patients for
10 an average of about five and a half.

11 And you can see the BSA at baseline was
12 comparable across the board.

13 If we look at slide 297 --

14 ACTING CHAIRMAN STERN: Could I ask a
15 question right there?

16 DR. LAWRENCE: Oh, certainly. Please. If
17 we could put slide 298 back, please.

18 ACTING CHAIRMAN STERN: To me it's very
19 interesting that, if I can read it, in adults -- I'm
20 sorry. I can't. Could you tell me what the -- I'm
21 not sure I can read whether that's six or what the
22 mean, the daily ointment use.

1 DR. LAWRENCE: The daily ointment use
2 during treatment in adults is about -- in adult
3 patients is 9.6 in vehicle and 6.2 and 6.4 in the
4 treatment group.

5 ACTING CHAIRMAN STERN: Okay. So about
6 six.

7 DR. LAWRENCE: Yeah, about six.

8 ACTING CHAIRMAN STERN: I'm sorry. It's
9 difficult for me to read.

10 DR. LAWRENCE: No, that's okay. I'm
11 having trouble, and I'm standing in front of it.

12 ACTING CHAIRMAN STERN: And I see that the
13 percent body surface area was nearly half the body.

14 DR. LAWRENCE: Yes, that is correct.

15 ACTING CHAIRMAN STERN: And this is a
16 twice a day application.

17 DR. LAWRENCE: Yes.

18 ACTING CHAIRMAN STERN: The usual rule of
19 thumb is that it takes about 15 to 30 grams to cover
20 in one application your entire body surface area, and
21 this is suggesting that you're using about three grams
22 each application to treat half the body surface area.

1 That actually comes to a question I had
2 earlier. I found this distribution of extent of body
3 surface area to be quite extraordinary for a clinical
4 trial. I think it was about 70 percent of individuals
5 had more than 20 or 25 -- more than 25 percent of body
6 surface area involved, and about 20 percent had more
7 than 75 percent of body surface area involved.

8 I'm wondering exactly how you documented
9 and counted body surface area because these are at
10 least in my clinical experience quite extraordinary
11 amounts of truly affected area for atopic dermatitis.

12 DR. LAWRENCE: If I could actually to
13 answer that question, let me have slide 390, please.

14 Again, these are the double blind studies,
15 the 12-week studies, and these are pooled data. You
16 can see here the distribution of baseline body surface
17 area, 30 percent, ten to 25, et cetera.

18 ACTING CHAIRMAN STERN: Right.

19 DR. LAWRENCE: And I don't need to read
20 them to you.

21 In overall about 46 percent of the
22 patients -- 46 percent of the patients BSA was

1 affected at baseline. I think one issue on the slide
2 for the exposure is the way we've calculated, it
3 artificially, I think, lowers it.

4 What we know is that as the patients get
5 better, the BSA decreases. The amount used on a daily
6 basis diminishes. When we calculate these numbers, we
7 take the total amount used, divide it by number of
8 days, and that's an average daily. So I think it's
9 probably a little bit of a misrepresentation. I
10 apologize for that confusion.

11 We know that you certainly see more in the
12 beginning and much less as the patients get better and
13 BSA decreases.

14 ACTING CHAIRMAN STERN: I guess though my
15 question was here. This is to me an extraordinary
16 distribution of extent even if you're looking for
17 severe individuals. I'm one of those individuals who
18 uses some of these other modalities to treat severe
19 atopic dermatitis, and the proportion of adults that
20 we see, in fact, with terrible atopic disabling
21 disease, who really at any given time have more than
22 half their body affected in terms of BSA, is quite

1 small, even in a very self-selected population of
2 people who have come to very invasive therapies.

3 So I just wondered how you could recruit
4 these individuals.

5 DR. LAWRENCE: I think maybe the best
6 thing there, Dr. Stern, Dr. Amy Paller is one of our
7 investigators, and I think she has a greater
8 familiarity with the calculations.

9 ACTING CHAIRMAN STERN: She's a
10 pediatrician though.

11 DR. LAWRENCE: Yes, but she has --

12 ACTING CHAIRMAN STERN: I'm more concerned
13 about the adults because these are really --

14 DR. LAWRENCE: Yeah.

15 ACTING CHAIRMAN STERN: In kids I've seen
16 it, but in adults it's quite extraordinary.

17 DR. LAWRENCE: It was. It was based on
18 the calculation of body surface area using a
19 homunculus, and the investigator's determination at
20 baseline. So, again, it was investigator driven. We
21 did not calculate those numbers.

22 I don't know though if it would be

1 helpful. Dr. Paller could comment on the severity of
2 the patients we enrolled. They were quite dramatic.

3 Amy, maybe you'd like to comment on that.
4 It's easier to -- unfortunately the room's acoustics
5 are not very good.

6 DR. PALLER: Yeah, the question is really
7 different here because Dr. Stern's question was about
8 adults, and my experience is pretty much exclusively
9 with children, where I think everyone would agree we
10 not uncommonly will see children who have extensive
11 body surface area involvement.

12 ACTING CHAIRMAN STERN: Could I ask other
13 panel members, you know, who take care of atopic
14 dermatitis if you see them very often with truly more
15 than half their body involved, not a patch here and a
16 patch there, but actual coverage?

17 DR. ABEL: Well, often when I see patients
18 with very extensive atopic dermatitis, those are
19 patients who often have superficial impetiginization.
20 they're excoriating, and their atopic dermatitis has
21 become more widespread, and those are also patients
22 who respond to systemic antibiotics.

1 And that brought up a question to my mind,
2 also relates to safety. How were these patients
3 assessed for infection, signs of superficial
4 impetiginization or infection, and how that would
5 relate to decreasing the risk of folliculitis,
6 bacterial superinfection, and all of the other.

7 I know this is separate questions mixed up
8 together, but I suppose also in response to Dr. Stern,
9 I think, and one reason for it to be widespread would
10 be secondary infection, but also these patients are
11 very xerotic. They have very dry, scaly skin, and
12 perhaps that's taken into account with assessment of
13 body surface area because sometimes, I mean, these
14 lesions, unlike psoriasis, are poorly marginated, and
15 there's diffuse involvement with xerosis.

16 So I think it might be difficult under a
17 number of circumstances to really define body surface
18 area, the way one would do it with psoriasis, where
19 there are discrete blacks (phonetic).

20 But I am interested in how patients were
21 assessed for infection. Were they treated with
22 antibiotics first? Do you exclude patients who have

1 active excoriations and crusting?

2 DR. LAWRENCE: We did not exclude patients
3 with excoriations or crusting. At the time of
4 enrollment in the study, we did exclude patients who
5 are actively infected, assessed by the managing
6 physician.

7 During the course of the study if they did
8 get infected, they were permitted to use systemic
9 antibiotics as part of the treatment, and as you saw
10 in the data that I presented, the number of skin
11 infections actually was quite similar across the three
12 treatment groups, vehicle and the two tacrolimus
13 treatment groups. It was running about 11 percent
14 total, which is, I would think, would probably be low
15 or in the range that you would anticipate with these
16 patients, especially chronically.

17 But we -- and certainly in the long-term
18 studies at least, the incidence rate of infection was
19 about 11 percent. We actually had a greater number of
20 skin infections in the patients in the 12 week study
21 in the vehicle group compared to the tacrolimus
22 ointment group.

1 As far as inter -- and I'm sorry. I have
2 trouble with that word -- the impend --

3 DR. ABEL: Secondary -- superficial
4 secondary infection.

5 DR. LAWRENCE: Thank you. That's much
6 easier, needless to say.

7 We did require that patients not be
8 actively infected at the time of enrollment. That was
9 just the decision we made because at that time we
10 didn't know what other issues may arise with the
11 treatment of the drug, and we were being, I think,
12 relatively conservative.

13 Did that answer your question or is there
14 anything else I can answer, Dr. Abel? I'll be happy
15 to try.

16 DR. ABEL: Well, in many of these,
17 oftentimes patients with severe, widespread atopic
18 dermatitis need systemic antibiotics. So I was
19 wondering how many have required that prior to entry
20 of the study.

21 DR. LAWRENCE: We only have data for the
22 30 days prior to the study. Most of these patients

1 had required, I will tell you from history, systemic
2 and topical antibiotics, systemic and frequently in
3 especially the adults systemic corticosteroids. So
4 these were very severe patients at baseline, and in
5 fact, if I could have slide number 820, that may
6 answer some of your questions.

7 ACTING CHAIRMAN STERN: There was an
8 exclusion criterion though about recent use of
9 systemic antibiotics.

10 DR. LAWRENCE: Right, exactly.

11 ACTING CHAIRMAN STERN: So these are not
12 individuals who at the time of enrollment --

13 DR. LAWRENCE: That is correct. Yes, that
14 is correct.

15 So what you can see here though is that
16 within the 30 days prior, a fair number of patients,
17 about eight percent, had taken systemic antibacterials
18 during that period. Again, you can see systemic
19 corticosteroids.

20 These were very severe patients, and were
21 certainly very difficult to manage obviously in the
22 baseline state.

1 Does that answer your question, Dr. Abel?

2 DR. ABEL: Thank you.

3 DR. LIM: I have a question on your slide
4 number 90, where you did say that this is the first
5 line therapy in adults and children of two years of
6 age.

7 Since you did not do a sort head-to-head
8 comparison between tacrolimus and the more traditional
9 treatment for atopic dermatitis, how did you come to
10 the conclusion that this should be used as a first
11 line therapy?

12 DR. LAWRENCE: I think, Dr. Lim, that
13 really is maybe partially a semantic issue. We
14 believe that this should be an option for patients who
15 require treatment for their atopic dermatitis and
16 should be one of the options available to physicians
17 at the time that they're making a determination.

18 The majority of our patients actually have
19 been treated for many years. Previously many of them
20 had actually failed previous conventional therapy.

21 I think the issue about the first onset of
22 disease, which would obviously only impact the

1 youngest of children, I think still we believe that
2 the safety and efficacy have been adequately
3 demonstrated enough that even the physician, we
4 believe, is in the best position to really make a
5 risk-benefit determination on which particular drug or
6 product would be appropriate for that particular
7 patient.

8 That's really how we're persisting in the
9 concept of first line therapy.

10 ACTING CHAIRMAN STERN: I'd like to ask
11 two last questions. One is since this is an often
12 lifelong disease, are safety data for one year
13 sufficient to feel confident about the long-term risks
14 of low dose exposure and localized exposure to this
15 immunosuppressive agent.

16 And the second, related to that, is --
17 perhaps Dr. Forges might address this -- is what might
18 be the models that might, in fact, address the issue
19 not of simultaneous UV and change in the risk of skin
20 cancer, but the risk of skin cancer with long-term use
21 in people who have had substantial prior UV or risk
22 characteristics, putting them at higher risk for non-