FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS
ADVISORY COMMITTEE

Friday,
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Ballroom
Hilton Hotel
620 Perry Parkway
Gaithersburg, Maryland

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S (1:00 p.m.)

DR. DRAKE: I would like to ask everybody to take their seat and please assemble.

Welcome to the Dermatologic and Ophthalmic Drugs Advisory Board meeting number 51. This is an open session regarding NDA 20-965, Levulan Kerastick for topical solution.

The first thing I will do is identify myself. I'm Lynn Drake. I'm professor and chair of the Department of Dermatology at the University of Oklahoma Health Sciences Center, and also hold a position of lecturer at Harvard Medical School, Massachusetts General Hospital.

I would like the panel to introduce themselves. I know you've done this before these last 2 days, but we have new players, so I would very much appreciate it if you would identify yourself by name and position, as well as what you do.

Dr. Stern, would you please start?

DR. STERN: Okay. I'm Robert Stern. I'm a professor of dermatology at the Harvard Medical School at the Beth Israel Deaconess Medical Center.

DR. MILLER: I'm Fred Miller. I'm director of dermatology at Geisinger Medical Center, Danville, Pennsylvania.

DR. DiGIOVANNA: John DiGiovanna. I'm director of the Division of Dermatopharmacology at Brown University, and an adjunct investigator at NIAMS of NIH.

MS. COHEN: I don't know what to say with all those things. I'm Susan Cohen. I'm a consumer member, and I also spend some time at the state attorney's office in Montgomery County.

DR. LIM: I'm Henry Lim, chairman of dermatology, Henry Ford Hospital, Detroit, Michigan.

DR. JORDON: Dr. Bob Jordon, professor and chairman, Department of Dermatology, University of Texas Medical School, Houston.

DR. McGUIRE: I'm Joe McGuire, professor of dermatology and pediatrics at Stanford University.

MS. RILEY: I'm Tracy Riley. I'm the secretary of the Dermatologic and Ophthalmic Drugs Advisory Committee. I'm with FDA.

DR. KILPATRICK: Jim Kilpatrick, professor of biostatistics at the Medical College of Virginia.

DR. MINDEL: Joel Mindel, professor of ophthalmology and pharmacology at Mount Sinai Medical Center, New York.

DR. LAVIN: Philip Lavin, a biostatistician with Boston Biostatistics, and on the faculty of Harvard Medical School.

MR. FELTEN: I'm not on the panel.

DR. DRAKE: That's all right. You're at the table.

MR. FELTEN: I'm Richard Felten. I'm the device reviewer for the NDA.

MS. FARR: Shahla Farr. I'm the biostatistical reviewer, FDA.

DR. OKUN: I'm Marty Okun, the medical reviewer for this NDA.

DR. WILKIN: Jon Wilkin, Dermatologic and Dental Division Director.

DR. DRAKE: Thank you.

I am going to announce a slight deviation in the order of business. Not in the order, but I want to announce the fact that we'll probably not take a formal break this afternoon in the interest of completing this

deliberation in a timely manner. So for those of you that need a break, please feel free to just sort of slip out and take one.

And I would like now to ask -- oh, I'm sorry. Dr. Abel just joined us.

Would you mind identifying yourself and your affiliation?

DR. ABEL: Elizabeth Abel, dermatology, clinical professor of dermatology at Stanford University.

DR. DRAKE: Thank you.

I'm now going to ask our executive secretary, Tracy Riley, to give the conflict of interest statement.

MS. RILEY: Good afternoon. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no

potential for conflict of interest at this meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. DRAKE: Thank you, Ms. Riley.

I'd like to ask Dr. Jonathan Wilkin to give his opening and introductory remarks about our business today.

DR. WILKIN: Thank you, Dr. Drake.

The questions for this afternoon are largely directed to labeling issues. The agency has already come to the conclusion regarding the approvability of this product. So I'll not read these in the interest of time at this time, but the committee has had these to

review.

DR. DRAKE: Thank you, Dr. Wilkin.

The committee has the questions before them and the issues presented before them, so what I'd like to do now is go to the open public hearing. We've had no written requests for appearances today; however, the invitation is open for anybody to approach the open mike that wishes to. If so, I would like you to identify yourself and any conflicts of interest or financial ties to the issue being discussed today.

(No response.)

DR. DRAKE: Seeing none, I think we'll move forward, then, with the rest of the program, and I would like to move now to the sponsor's presentation. It's DUSA Pharmaceuticals, and are you Samuel Swetland?

MR. SWETLAND: Yes.

DR. DRAKE: Hi. Welcome. I would ask you to introduce yourself and all your fellow presenters, as well as your role.

And first thing, would you tell me what D-U-S-A stands for?

MR. SWETLAND: D-U-S-A is DUSA, and that's

the name of the company.

DR. DRAKE: That is the whole name of the company?

MR. SWETLAND: DUSA Pharmaceuticals, Inc.

DR. DRAKE: Thank you.

MR. SWETLAND: Thank you.

I'm Sam Swetland of Guidelines, Inc. I am a regulatory consultant for DUSA Pharmaceuticals, and today we are here to discuss -- the first slide, please -- today we're here to discuss DUSA Pharmaceuticals' NDA for Levulan Kerastick for topical solution, 20 percent --

DR. DRAKE: Can you excuse me just one moment?

We need to have that off. There you go. Thank you.

MR. SWETLAND: NDA No. 20-965.

The Levulan Kerastick in conjunction with the BLU-U blue light photodynamic therapy illuminator comprise a drug/device combination product. The primary mode of action for the combination product has been determined to be that of a drug, and the Center for Drug

Evaluation and Research has been given administrative jurisdiction over the combination product. However, the Center for Devices and Radiological Health has review responsibilities for the premarket approval application for the device component.

This is a slide of an outline of the sponsor's presentation today. I will present some housekeeping issues and a brief introduction to the Levulan Kerastick NDA. Following my presentation, Dr. Stuart Marcus of DUSA Pharmaceuticals will present an overview of the Levulan photodynamic therapy. Next, Dr. Allyn Golub, also of Guidelines, Inc., will present the pharmacology and toxicology information that was submitted as part of the NDA. Then Dr. Marcus will return to present the Phase I and Phase II clinical study. Our last speaker today will be Dr. Daniel Piacquadio of Therapeutics, Inc., and the University of California at San Diego. He was one of the clinical investigators in our Phase III program, and Dr. Piacquadio will present the Phase III clinical data for the Levulan Kerastick.

This slide just gives a few definitions for

some terms that will be used throughout our presentation. Levulan is the registered trademark for DUSA Pharmaceuticals' brand of the active drug substance, aminolevulinic acid hydrochloride, or ALA HCl. The Kerastick is the trade name for DUSA's topical applicator dosage form. BLU-U is the trade name for DUSA's blue light photodynamic therapy illuminator. ALA will be used to refer to the endogenous form of aminolevulinic acid. And, finally, PDT stands for photodynamic therapy.

The Levulan Kerastick for topical solution, plus blue light irradiation using the BLU-U blue light photodynamic therapy illuminator, is indicated for the treatment of actinic keratoses of the face and scalp. The drug component of the combination product is the Levulan Kerastick. The Kerastick was specifically designed to segregate the active drug powder from the topical solution vehicle during distribution and storage, and to allow the rapid-add mixture of the two components just prior to its use.

Since this is a novel dosage form, we brought along a display containing the various components of the

Kerastick, and we'll just pass a few of those around the room. In the meantime, this is a picture of the display.

The Kerastick is comprised of a dermatological applicator tip and a flexible plastic applicator tube containing two sealed glass ampules. The glass ampules contain the appropriate amount of the active drug substance and the topical solution vehicle, when mixed together, to produce a 20 percent weight/volume topical solution. The glass tubes inside the applicator are shown over here on the right. This is placed within a protective cardboard sleeve, with a cardboard cap that covers the applicator tip during shipping and storage.

The drug application is conducted in the physician's office by the physician or health professional, and at the time of administration the two glass ampules are crushed through the applicator sleeve by pressing at the locations printed on the label, and the contents are mixed by shaking. Then the cardboard cap is removed, and the solution is applied to the target lesion by gently dabbing the lesion with the tip

such that it wets the lesion, but does not drip or run.

The second component of the drug/device combination is the BLU-U blue light photodynamic therapy illuminator. Pictured here is one of the clinical units that was used in the Phase III clinical trials. The BLU-U is a compact non-laser light source that was specifically designed to provide uniform distribution of blue light to the patient's face or scalp at a nominal wavelength of 417 nanometers and a power density of 10 milliwatts per centimeter squared. A premarket approval application has been submitted to CDRH and has been reviewed by that center.

Now I'd like to turn the presentation over to Dr. Marcus to describe how these drug and device components will be used in Levulan photodynamic therapy.

DR. MARCUS: Thank you, Mr. Swetland.

I'm going to introduce the section of this presentation dealing with the photodynamic therapy using Levulan and blue light. The first part will discuss the background mechanism and the pharmacokinetics, as well as dose administered and pharm/tox. The second part will discuss the Phase II clinical trials, which

involved both drug dose ranging and blue light dose ranging. And, lastly, there will be discussion of the pivotal clinical trials utilizing the Levulan Kerastick and the blue light source.

ALA, aminolevulinic acid, is an endogenous molecule, and it's not a new molecule, but in the form of Levulan, it is a new chemical entity and a new drug. There is an extensive worldwide literature on photodynamic therapy using topical and systemic aminolevulinic acid hydrochloride, and this molecule is rather unique in that there are two clinical conditions which may be looked upon as human models of chronic exposure to systemically overdose ALA and protoporphyrin, acute intermittent porphyria for chronic overdosing of systemic ALA and porphobilinogen, and erythropoietic protoporphyria as a model for chronic lifetime overdosing of protoporphyrin-9.

Photodynamic therapy is a type of photochemotherapy, which is a two-stage process, in that the photosensitizer is delivered and then activated by light. However, photodynamic therapy differs from other forms of photochemotherapy by its requirements for

oxygen. The therapeutic effects of photodynamic therapy are thought to be due to the production of singlet oxygen through the transfer of light energy through the photosensitizer to ground-state oxygen.

Using an endogenous photosensitizer such as ALA involves the following steps: Levulan is taken up by cells, converted first to ALA and then to protoporphyrin, which is a potent photosensitizer. As it accumulates, cells such as precancerous, malignant, or fast-growing cells can be identified by a characteristic fluorescence of protoporphyrin-9. And then if you expose those cells which accumulate protoporphyrin-9 to an intense light of appropriate wavelength and energy, the PDT effect occurs, leading to cell death. In the case of Levulan PDT, the selective therapeutic benefit occurs due to selective drug application, followed by the accumulation of protoporphyrin-9 in the target cells.

This is the heme pathway, showing aminolevulinic acid as the first committed molecule in that pathway. The control point for the pathway is the regulation of ALA synthesis through ALA synthase

regulation by the molecule heme, which is above the screen. When ALA is added exogenously, it bypasses the control point, and enzymes which are constitutively present, represented by the red line, are converted to protoporphyrin-9, which, through the addition of iron by ferrochelatase, becomes the non-photosensitizing molecule heme.

This is a simplification of protoporphyrin-9 accumulation, which we like to call the Levulan therapeutic pathway. It shows the Levulan Kerastick applying ALA hydrochloride to the skin surface, which then becomes ALA and enters the system after the control point. It's then rapidly converted to protoporphyrin-9. Protoporphyrin-9 builds up rapidly, exceeding the capacity of ferrochelatase to remove it, and, therefore, accumulates within the system when light is then shone on the system, such as the BLU-U. The therapeutic benefit occurs through the production of singlet oxygen.

But one must remember that ferrochelatase provides an escape mechanism by which excess protoporphyrin-9 is rapidly converted, then, to heme, which is a non-photosensitizer. Also, the very active

shining of light on protoporphyrin-9 for PDT produces a photobleaching effect, removing excess drug.

I'd like now to introduce Dr. Allyn Golub, who will speak.

DR. GOLUB: Thank you, Dr. Marcus.

My presentation today will be divided into two sections. First, I'd like to discuss the pharmacokinetics/ bioavailability and how we estimate the dose of Levulan that's administered topically. Secondly, I'll briefly discuss the preclinical toxicology studies that were conducted with this compound.

As Dr. Marcus indicated, aminolevulinic acid is a well-described endogenous compound that's found in virtually all living organisms as a precursor in the porphyrin biosynthetic pathway leading to the formation of heme and chlorophyll.

For pharmaceutical purposes, we use the hydrochloride salt of aminolevulinic acid, just known as Levulan. This is an odorless, white to off-white crystalline powder with a molecular weight of 167.59. It's freely soluble in water, slightly soluble in

alcohol, and practically insoluble in most organic solvents. The drug completely dissociates in aqueous solution, leading to a solution with low pH. The primary degradation product in solution is pyrazine 2,5-dipropionic acid that's formed by the autocondensation of two aminolevulinic acid molecules.

The vehicle for Levulan administration is comprised of common dermatological excipients and has about 50 percent alcohol.

Studies were done in both humans and dogs to characterize the systemic bioavailability and pharmacokinetics of Levulan to basically confirm what's already well described in the literature. In this particular slide, we're showing the results from a study in six normal male volunteers who were administered 128 milligrams of Levulan intravenously and orally, and the time concentration curve generated over a period of 8 hours. The important information on this slide is that the drug is very rapidly cleared from the systemic circulation that occurs following both intravenous and oral absorption, and that the oral bioavailability is lower than the area under the curve for the intravenous

dose; in fact, it's about 60 percent bioavailable in this particular study.

This table summarizes the results from that human study as well as a dog study. The IV half-life here was about 50 minutes, very rapidly excreted. In the dog it was about 20 minutes. The PO half-life was about 40 minutes in both species. And the relative bioavailability, as I said, was 60 percent in the humans in that study, and about 40 percent in the dogs.

I should mention that we also monitored protoporphyrin levels in this study. The levels were very, very low, they were erratic, and beyond 12 hours they were undetectable at the limits of the sensitivity of the assays that we used.

Based on the wealth of data that we've generated in our developmental process, we're able to estimate the amount of Levulan that would be administered topically using the Kerastick as directed in the package insert and its potential systemic availability. From in vitro studies, several that were done during product development, we've calculated that approximately 2 milligrams per centimeter squared of

Levulan will be applied in two successive applications as directed in the package insert.

In our Phase II studies, ALA-007 and -017, we carefully measured the AK lesion surface area that was randomly chosen for application of the drug. This turned out to be approximately half a square centimeter per lesion. In our Phase III studies, ALA-018 and -019, physicians were allowed to apply the drug to four to 15 lesions per patient. Seventy-five percent of the applications were less than 10 lesions, but we're going to err on the high side and assume, let's say, 15 lesions are applied per patient. As a matter of fact, all of these values were chosen to be on the high side of the numbers that we calculated.

So simply by multiplying the quantity of Levulan applied times the lesion surface area that it's being applied to, times the total number of AK lesions treated, we can calculate that approximately 15 milligrams of Levulan would be applied per patient, and that's equivalent to about 12 milligrams of ALA. You divide that for a 70-kilogram individual, and it indicates that less than .2 milligrams per kilogram of

aminolevulinic acid would be applied to the patient.

Now, we've done in vitro studies through cadaver skin, again, using exactly the methodology described in the package insert for application in the Levulan topical vehicle, both to intact and stripped cadaver skin, in which the stratum corneum was removed. In intact skin, we see about -- and this, again, is on the high side -- approximately 2 percent of the drug passes through the skin into the receptor fluid over a 16-hour dosing interval. In stripped skin, in which the stratum corneum is totally removed, we see upwards of 30 percent over 16 hours. However, even if we assume 100 percent of that 12 milligrams of ALA is absorbed systemically, we calculate that that would be only about 3.5 percent of this number, 350 milligrams per day, which is believed to be synthesized by the human body to support endogenous heme synthesis.

With these numbers in mind now, let's turn to the preclinical toxicology program that was conducted for the drug.

Acute toxicity studies were initially done in mouse, rat, and dog. In mice and rats, doses up to 300

milligrams per kilogram were administered intravenously with no adverse effects. This was a standard battery of measurements that was used to characterize the -- these studies were GLP studies. In the dog, 100 milligrams per kilogram led to some excessive salivation and vomiting and transiently increased aspartate and alanine aminotransferase activities, particularly at the 100-milligram-per-kilogram dose. These increases were judged to be mild to moderate and were very transient, lasted for a very short period of time.

In the skin studies that were conducted with this product, we did subcutaneous administration of the drug up to 1,000 milligrams, a gram per kilogram, and found dose-dependent irritation and/or the formation of lesions at the site of injection. There were no other systemic findings made, and these effects were judged to be a result of the high ionic strength and low pH of the solutions that were administered.

In rabbits, we have evaluated topically the effects of the topical solution and the topical cream. The results in both of these studies, up to 30 percent ALA showed slight to moderate dermal irritation with

both the vehicle and the formulation.

I'd like to focus a little bit further on this study, the topical solution, because this is the product that's under consideration here.

There were 20 male and 20 female rabbits in the study. The body weight was approximately 2 kilograms. The drug application area was over 180 square centimeters on the back of the animal. The skin was prepared by clipping it free of hair, and then the epidermis was abraded to allow penetration of the drug through the stratum corneum. As I indicated, doses up to 30 percent of the topical solution were applied. It was applied at a dose of 2 grams of the solution per kilogram of animal body weight under occlusion. There was no light exposure in the study, but the skin was completely occluded for a period of 24 hours.

This table summarizes the results found in this study. You see even with vehicle there was slight to moderate erythema. That tended to increase to moderate at the highest concentration. There was some edema, desquamation, and coriaceousness and fissuring actually occurred primarily at the highest dose. In

general there was only slight to moderate irritation detected in the study under pretty stringent conditions, under occlusion for 24 hours.

Finally, a battery of mutagenicity protocols has been conducted with the Levulan product. This includes the salmonella, E. coli, and mammalian microsome reverse mutation assay, which is also known as the Ames test, at doses up to 5,000 micrograms per plate, plus or minus metabolic activation. The end result of this study was that there was no increase in revertants.

I should mention this says, "with a confirmatory assay." All of these assays were done twice in succession, a complete replicate of the study, just to confirm the results obtained the first time.

Similarly, an Ames test with solar light radiation to look for photoproducts of ALA during incubation was conducted up to 5,000 micrograms per plate. Again, no increase in revertants, with or without solar light radiation. Mouse lymphoma also was negative, plus or minus metabolic activation. There's no evidence in these studies that there is mutagenicity.

And, finally, in the in vivo mouse micronucleus assay, not only was there no increase in micronuclei, indicating low or no potential for genotoxicity, but also the dose of 1,600 milligrams per kilogram was well tolerated by the animals in the study. So overall it showed a very comfortable side effect spectrum.

Now I'll turn the program back to Dr. Marcus, who will describe the Phase I and II studies that were done with this compound.

DR. MARCUS: Thank you, Dr. Drake, and thank you, Dr. Golub.

I'll be starting off the clinical data summary with the controlled clinical trials that were used to support and define the Phase III pivotal study.

The first was a Phase II light dose ranging study using blue light and 20 percent topical Levulan solution. ALA-007's study design was of a randomized, vehicle-controlled, and investigator-blinded multicenter study in which the Levulan solution was applied to individual AK lesions on 36 patients. There were three clinical trial sites, and because two lesions were treated with either Levulan or vehicle, the complete

patient response was judged to be as patients with 100 percent of AK lesions cleared.

At Week 8, which is the primary efficacy time point, there is a trend, as you can see. The blue light doses were 2, 5, and 10 joules per square centimeter, delivered at either 3, 5, or 10 milliwatts per square centimeter power density. If you look at the 10-milliwatts-per-square-centimeter bar, you see a trend toward a dose/response with a maximal dose/response of 80 percent after a single treatment with light and drug.

The summary of this study showed, again, up to 80 percent of patients completely responded to a single treatment with topical Levulan and blue light, and 10 joules per square centimeter delivered at the highest power density provided the best results in that study.

In the safety profile, mild to moderate stinging and burning was observed, mostly during light treatment, and this will prove to be a constant throughout the studies you'll be seeing this afternoon. There were no treatment-related significant adverse events and no systemic photosensitivity observed.

Another blue light dose ranging study was done as a safety study, ALA-016. Again, this was a randomized, vehicle-controlled, investigator-blinded multicenter study, with 64 patients randomized. Here the 20 percent Levulan solution was applied to a 25-square-centimeter area of skin containing three to seven AKs, photodamaged skin. There were three clinical sites, as before, and here, because of the larger number of AKs treated, we were able to define the complete patient response as patients having greater than or equal to 75 percent of their lesions completely cleared.

The results of this study show that, again, if you look at the 10-milliwatts-per-square-centimeter bar, we saw 100 percent responses in all three doses of light, but the most consistent result was 100 percent response at 10 joules per square centimeter.

In this study, up to 100 percent of the patients, by our definition, completely responded to a single treatment with topical 20 percent Levulan and blue light. Again, 10 joules per square centimeter gave the best result, and this, of course, was consistent with the first blue light dose ranging study.

In the safety results -- and this was done as a safety study -- there was stinging and burning during light treatment, and there were no treatment-related significant adverse events or systemic photosensitivity. However, the discomfort of stinging and burning was increased as a result of applying Levulan 20 percent solution to a larger area than single AKs, individual AKs, and in this study 6 percent of the patients had PDT treatment terminated early, and 9 percent reduced the power density due to the discomfort of stinging and burning as a result of the larger-area application. We took that as support of the labeling statement to apply Levulan solution to individual AKs.

A Phase II drug dose ranging study was carried out using blue light at 10 joules per square centimeter, delivered at 10 milliwatts per centimeter. In this study, we evaluated the safety and efficacy of Levulan topical solution at 2.5, 5, 10, 20, and 30 percent weight-to-volume solution. Again, this was randomized, vehicle-controlled, and investigator-blinded, and multicenter, but this one was the first study statistically sized to detect the difference

between Levulan 5 percent and Levulan 20 percent solutions. One hundred and twenty-four patients were accrued to this study from eight clinical trial sites.

Next.

Here are the efficacy results, graphed by both lesion response rate and patient response rate, using patients who have greater than or equal to 75 percent of their lesions completely clearing judged as patient complete responders. As you can see, there is a dose/ response evident in the study, with a plateau emerging at 10, 20, and 30 percent. For the patient responders, the best dose was 20 percent in this study.

All three 10, 20, and 30 percent Levulan solution concentrations were significantly better than the 5 percent solution, and that's shown here.

In the safety study, because of a larger number of patients, we were better able to characterize the stinging and burning, and, again, there was primarily stinging and burning during the light treatment, but it was very subjective. There was no clear drug dose/response. It was also transient and resolved rather rapidly on the termination of light

treatment. There were no treatment-related significant adverse events and no systemic photosensitivity again, and the fact that there was no clear drug dose/response to the burning and stinging is shown by the fact that two patients out of 124 had their PDT treatment terminated early for discomfort, or burning and stinging, but one had 2.5 percent Levulan applied and one had 20 percent.

We were also able to objectively characterize what is termed the PDT response to Levulan PDT, and it consists of lesional erythema and edema, which peak 24 hours after the light treatment, it's transient, and rarely, if ever, requires medication.

The conclusion from these Phase II studies was that we would use Levulan 20 percent topical solution and blue light at a dose of 10 joules per square centimeter, delivered at 10 milliwatts per square centimeter, for the Phase III pivotal trial.

I'd like now to call Dr. Dan Piacquadio to discuss the Phase III clinical trial design, safety, and efficacy results.

DR. DRAKE: Dr. Lim, you have a question for

clarification?

DR. LIM: Clarification, yes.

On the 016 and 017 study, you have, I think, six patients and two patients stopping treatment before treatment was completed because of the stinging sensation. Were those patients included in your data analysis, or were they dropped from data analysis?

DR. MARCUS: They were dropped from that data analysis of that study. But I think we'll have a fuller report of all patients in the Phase III study.

DR. PIACQUADIO: Thank you.

I'll apologize in advance for any coughing or hacking. I have a bit of a cold with postnasal drip, but I think we'll be all right.

I have the pleasure today to present the data for this trial. It's unusual to have the chance to talk about a new class of therapy in dermatology, and I appreciate the opportunity for DUSA Pharmaceuticals inviting me to speak here today.

Basically this pivotal trial was divided into two Phase III studies of photodynamic therapy with Levulan topical solution and visible blue light in the

treatment of multiple actinic keratoses of the face and scalp. The objective of these two pivotal studies was to prove the safety and efficacy of Levulan 20 percent solution and the 10-joules-per-centimeter-squared blue light delivered at 10 milliwatts per centimeter squared in the treatment of multiple actinic keratoses, again, of the face and scalp.

I'll now talk about a few of the key elements of the design. These Phase III studies were vehicle-controlled, investigator-blinded, multicenter, randomized, uneven parallel group studies in patients with multiple AKs of the face and scalp. The aggregate enrollment was 243 patients for both trials, and, again, all qualifying with four to 15 target lesions on the face or scalp area.

This is an outline of the procedures throughout the trial. There are a few key points of note. The duration of the trial was 12 weeks. There were two treatment opportunities, one at baseline and another at Week 8. The Week 8 treatment point was for those lesions, be it active or vehicle-treated, that did not fully respond. And then during the course of the

study, adverse events in PDT response were documented at every visit.

With respect to both of these trials, a very experienced group of clinicians well known for their activity in the clinical research arena was incorporated into both trials, and they represented a diverse geographic distribution as well.

Now we're going to review some of the highlights of the key inclusion and exclusion criteria that were applied. In this trial, male or non-pregnant female outpatients over the age of 18 years were enrolled. Females were either postmenopausal, surgically sterile, or were using an acceptable form of medical contraception and had a negative urine pregnancy test to enter the trial. And, again, they all met the same criteria of having four to 15 target lesions on the face or scalp.

With respect to key exclusion criteria, patients with a history of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins, or photodermatosis were excluded. Any use of photosensitizing drugs and very thick or markedly

hyperkeratotic actinic keratoses were excluded. Now, the AKs were graded on a scale of 1, 2, and 3. Moderately hyperkeratotic lesions were treated, and we'll see some photos of those cases.

Primary exclusion criteria regarding use of other therapeutic modalities before entry in the trial are highlighted here. Within a 2-week period, topical medications such as steroids, alpha-hydroxy acids, or retinoids were excluded. Within 4 weeks, systemic steroid therapy was precluded, and within the 2-month category, cryotherapy, laser therapy, chemical peel, topical 5-FU or Actinex treatment, systemic treatment with chemotherapeutic agents or any other immunomodulating drug or systemic retinoids were excluded.

Now we're going to talk a little bit about the activities at some of the key visits throughout the trial. One of the things to note in this trial design is, since PDT is an obvious therapeutic event, you can usually see it, this study design incorporated the use of both unblinded as well as blinded investigators. For this initial Baseline Visit A, which occurred 14 to 18

hours prior to light treatment and within 2 weeks of the original screening visit, again, the four to 15 target lesions were identified. They were numbered, documented, and graded by the evaluator, and photographs were also taken. Then, at that point in time, any PDT-like characteristics were evaluated.

The next activity at that visit was for the unblinded investigator only. Key activities included drug or vehicle application as per the protocol, which we'll talk about in a moment. Concomitant medications or adverse events were noted. And, most importantly, the patients were told to avoid light exposure and not to wash the areas where the drug was applied.

This is a demonstration of the application, and as Sam had talked about before, it's a pretty simple tool to use. There are two marking points on this cylinder that show you where to break the two ampules within it. Then you shake for a period of 2 to 3 minutes to mix the drug adequately, and then you basically simply dab on each actinic lesion individually, and in this trial that procedure was performed twice for each of the individual lesions. It

was very simple, easy to control, well tolerated by the patients.

Now we're moving on to the Baseline Visit B activities. Again, you should note that this is an unblinded investigator activity. This is referring to the pretreatment assessment, which is basically 14 to 18 hours after application of Levulan. At that time clinical signs of cutaneous reactivity with respect to erythema, edema, stinging and burning were evaluated on the 0 to 3 scale, shown here. Similarly, at that same visit, again, by the unblinded investigator, patients' subjective evaluation of stinging and burning intensity associated with the target lesions was graded on a similar scale, 0 to 3, none, mild, moderate, severe.

Now with respect to the light treatment aspect of this visit, again, performed by the unblinded investigator, the target lesions were rinsed off, then patted dry, and then they all received the uniform light treatment as specified in the protocol, the 10 joules per centimeter squared at a power density of 10 milliwatts per centimeter squared, for approximately 1,000 seconds, or 16 minutes and 40 seconds, of

treatment light time.

This is an example of a patient receiving light therapy. You can see a nice, uniform application of light over the treatment zone, which is the face in this case. In general the light is actually very easy to use and convenient for the patient as well.

Moving on to Baseline Visit B for the unblinded investigator with respect to actually characterizing the PDT response, there were two key areas of note, objective and subjective criteria, looking at the clinical manifestations of the PDT response reviewed earlier as well as by Dr. Marcus, and then the subjective assessment of stinging and burning. With respect to the stinging and burning, that assessment was done temporally during the entire treatment at 1, 6, and 11 minutes. Later when we start talking about the actual data results, if a patient had a severe notation at one of the time frames, they were frequently amalgamated or talked about having a severe burning or stinging response.

But what's important to note is that this is a temporal event, and actually when you treated these

patients, in general the reaction from a stinging and burning perspective was really mild to moderate. It was very unusual to have a patient react such that they wanted to discontinue the treatment. In fact, there were only six subjects throughout the trial.

Another problem here is the variability of the definition of what severe, moderate, mild means. There were no definitions given, and this is not a "professional" evaluator, it's a patient, and we all know the variability of what that definition or word means to each person.

Additionally, and lastly, at this visit other PDT-like reactions -- crusting, scaling, et cetera -- were also evaluated.

Follow-up visits were at 24 hours, as well as at Week 1, 4, 8, and 12, respectively. Efficacy evaluation, again, was the domain of the blinded investigator, performed at Week 4, 8, and 12, and, again, to assure the blinding, separate case report forms were used here so that that evaluator had no knowledge of the unblinded investigator's activity in the trial. Assessments of the PDT response were also

done, as well as adverse events and concomitant medications.

Now we're going to talk about the efficacy parameters for this study. The primary efficacy parameters are highlighted in this slide. Basically we're looking at lesion counts performed at baseline, as well as follow-up visits at Week 4, 8, and 12, respectively. And for the purposes of this trial, the protocol defined Week 8 as the primary temporal efficacy endpoint. Analyses included the percent of lesions that completely responded, the percent of patients that had a 75 percent or greater reduction in their lesion count, and the percentage of patients with 100 percent reduction in their lesion count.

I'll take a moment here to sort of clarify this nomenclature. It's a little confusing the way the term "complete response" is used in the protocol. In general when people think of complete response, they think of cleared. In this first category, that's what complete response really refers to, basically clearing of the lesion. The other two criteria refer to, of the lesions in that patient, four to 15, did 75 percent or

greater or 100 percent of them totally clear? And we'll review that when we go to the charts for the efficacy results.

Secondary efficacy parameters included the cosmetic response of each lesion, again, evaluated at Week 4, 8, and 12. The overall cosmetic response of each lesion was, again, graded on a four-point scale, from excellent to poor, as shown. And the patient evaluation of cosmetic response was also performed, but only at the Week 12 time point.

Now, for those patients that did not have all their lesions completely respond, be they drug-treated or vehicle-treated, they were retreated at Week 8 using the same methodology as the baseline visit that we reviewed earlier. These patients also had repeat follow-ups at 24 hours, as well as one week later, at Week 9.

Now, the importance of this slide is it shows the disposition of patients in both pivotal trials. Of note, I think, there were 243 patients enrolled, of which only 10 in aggregate discontinued from the trial. Whenever you have a trial that really only has a

therapeutic intervention of benefit sort of at the beginning of the trial and nothing for 12 additional weeks, to have a dropout rate in the range of 4 to 5 percent is pretty unusual.

The other thing to note here in this trial is that the distribution of dropouts for both the vehicle and Levulan treatment categories were essentially equivalent, and, similarly, there was no real trend with respect to the reasons for discontinuation in either of the groups, be they vehicle or active.

Now, this is a bar chart that summarizes the efficacy results per the protocol. What we have here on the X axis is the 018 data and the 019, and then the pooled data of both studies together. This goes to the issue of a little bit of confusion, at least for me, with respect to nomenclature, using this term "complete response" that has a variety of definitions. I think it's easier to view this as the response percentage based upon two criteria that are outlined to the right. The turquoise-colored bar refers to those patients where 75 percent or more of all the lesions treated in that individual, be it four to 15, cleared. The brown

color refers to those groups of patients where 100 percent or all of the lesions treated in those patients completely resolved. And similarly for the vehicle-controlled groups that are pink and yellow, respectively.

Key points of note on this chart, from my viewpoint, are as follows. There is basically good agreement between the two pivotal trials for both the active treatment groups and the vehicle treatment groups. There is obviously a marked statistical difference between active and vehicle for both studies. Essentially there is approximately a 77 percent response rate when one applies the greater-than-or-equal-to 75 percent criterion. With the more stringent 100 percent criterion, the rate decreases to approximately 66 percent. And the vehicle response rate, irrespective of what criterion is applied, is somewhere in the range of 10 to 18 percent.

Now, I know there was a question posed by the agency regarding the use of these different criteria, 100 percent and 75 percent. As a developer in the realm of dermatology, it's very rare for us to have great

therapeutics where the reasonable clinical endpoint as a doctor is complete resolution. The reality is, most tools we use in dermatology are modest in their therapeutic intervention. However, when you're trying to fully characterize the performance profile of a drug, it is very helpful to know what is the complete resolution as an endpoint. As a clinician, though, most drugs that we use, the expectation clinically is a very good clinical response, which would probably be, again, in that area of 75 percent or so.

So to me both of these variables are very important. One, if I'm trying to really get a handle on the performance index of the drug and want to know what it does as a perfect therapeutic intervention, the 100 percent criterion is extremely helpful. As a clinician practicing my craft, the idea of what does that 75 percent level mean is probably more important to me, because that gives me an idea of what's reasonable clinical expectation for using that therapeutic modality and understanding and making a best-choice decision for my patient.

Now, this is the data for Week 8, and now

we're going to move on to the longer time point, which is the Week 12 evaluation. Again, the presentation of the data is the same. On the X axis, the 018 data and the 019 data separate, and then pooled together. The Y axis, again, viewing it as response percent, and the two different criterion are 75 and 100 percent, respectively. Very similar in that we see relatively consistent agreement between the two trial groups in the marked difference between active and any vehicle effect, and in the pooled data response, with respect to the criterion of 75 percent or more, roughly about an 89 percent response. Applying the 100 percent criterion, we see approximately a 72 percent response.

Now we're going to look at a few clinical photos. This is an actinic keratosis in the preauricular area. This would be typical of a Grade 2 lesion. It is moderately hyperkeratotic.

The next slide we're going to look at shows the response 24 hours after therapy, and this is a pretty classic PDT-like reaction, with diffuse erythema surrounding the lesion area, maybe scant edema, and in this particular case, a small amount of superficial

erosion. Now, these characteristics resolve pretty quickly. Healing is usually over several days, with complete resolution of any type of sign or symptom usually within about a week.

This is the same patient at a Week 12 time point, and we can see the area is resolved, with no residual actinic keratosis remaining.

This is another patient that has a well-marginated, but rough hyperkeratotic lesion that has a nice juxtaposition to her hairline, to identify its location. Here, again, at 24 hours we see a similar PDT reaction, with scant erythema, probably a little less erosion, and maybe some trace edema. And then this is the Week 8 time point, which was the primary evaluation time point. There is no residual remaining.

This is the final case. The lesion is right here. It sits between the hairline and these two landmarks, to help orient everyone. Here we see a similar response, no erosion, but you can see there's a little more diffuse area involved with erythema, and potentially a little edema. And then, again, here is the 12-week time point, resolution of the lesion.

A summary of the secondary efficacy parameters with respect to cosmesis, we can look at the investigator-rated cosmetic response being graded as excellent or good. I believe these data are reversed. The 018 is actually 94 percent, the 019 is 90 percent, with an average of basically 92 percent, equivalent between the two trials. With respect to patient evaluation at the Week 12 time frame, again, 93 to 94 percent, respectively, for the 018 and 019 trials, a high degree of correlation between the two evaluators, experts and subjects.

With respect to safety summary for the two trials, the burning and stinging was reported during PDT, and it peaked during the first minute. Light treatment was discontinued in two of 88, or 2 percent, of the Levulan-treated patients in 018, and four of 93, or 4 percent, of the Levulan-treated patients in 019. No significant treatment-related adverse events were appreciated, and, similarly, no systemic photosensitivity was appreciated.

With respect to the PDT response with regard to erythema, it was present in a great majority of

patients at baseline. After light treatment, 99 to 100 percent of the patients had erythema, but it quickly resolved to near-baseline levels by Week 1, and the majority of it resolved over a few-day period.

With respect to edema, it was present in a far less number of patients, less than 1 percent, at baseline. After light treatment, it was seen in 28 to 41 percent of patients, and the edema also resolved to near-baseline levels after one week post-light treatment.

This slide characterizes the evaluation for pigmentation. It basically looks at pigmentary changes compared to baseline, which is not shown, at the Week 8 and Week 12 time point. Of real note here is that in general the preponderance of lesions, both in the active Levulan group as well as the vehicle group, have really no significant change in pigmentation. So from a therapeutic side effect standpoint, this therapeutic intervention has no net effect on pigmentation.

So in summary, looking at this first bullet, this applies to applications of that criterion that refers to 75 percent or greater response rate. Seventy-

seven percent of patients completely responded to Levulan PDT by Week 8 post-treatment, increasing to 89 percent by Week 12. If we apply the more stringent criterion of 100 percent, these numbers change to about 66 and 72 percent, respectively, for Week 8 and Week 12.

Consistent PDT responses were burning and stinging during light treatment and transient post-PDT lesional erythema and edema, which, again, resolved at the baseline levels within one week.

The cosmetic response is deemed to be good or excellent by the investigators in 92 percent of the lesions, and that number is in agreement with what the patients predicted or assessed as well. And, again, no pigmentary changes were seen as a result of therapy.

I thank you for your attention.

DR. MARCUS: This concludes the sponsor's presentation.

DR. DRAKE: I'd like to thank all the sponsor's presenters, and I thank you for being cognizant of the time. That was a very thorough presentation, and right on the button time-wise, and it was clear. So we appreciate it.

I would like to ask for some questions now. I'd still like to keep this on the clarification part until we get to the actual discussion phase, but I would like to call for clarification questions.

Dr. Lim?

DR. LIM: Yes, a clarification question for Dan.

Dan, on the clinical slides, there are two slides, I believe, where there is erythema following treatment on an area that appeared to be beyond the lesion site. Do you know if that is the effect of the ALA on normal skin, on clinically normal skin, or is it the effect of ALA on probably a subclinical lesion?

DR. PIACQUADIO: We're waiting to get the mike turned up, I guess.

DR. DRAKE: It's on.

DR. PIACQUADIO: If you look at that dab-o-matic tip, which I'm happy to pass around, it does have a surface area that's bigger than many AKs, so by using that tip, you're absolutely getting drug applied to the lesion as well as perilesional skin.

As you know as well as I do, AKs are a

manifestation that is clinically seen at one point, but is a continuum, and the adjacent skin especially in patients enrolled at my site is probably markedly photodamaged, whether you can clinically assess an AK or not.

So to your question in specific, I think what you're seeing is a combination of things. You may be seeing a true therapeutic selective effect in some patients that is related to an AK treatment that's subclinical. In some other patients, you have an inflammatory cascade that is not totally respecting the area of drug application and extends somewhat out beyond that.

DR. LIM: Thank you.

DR. DRAKE: Dr. Stern?

DR. STERN: To follow up on that question, do you have Phase I data in normals looking at the erythema effect of this application of agent in non-sun-exposed normal volunteers with these doses of light? I think that will tell us at least whether we have to be concerned about this being applied, even inadvertently, to areas that aren't sun damaged.

DR. MARCUS: We have not specifically done studies on areas that are non-photodamaged.

DR. STERN: There was never any dosimetry done in terms of normal skin and erythema with this topical agent?

DR. MARCUS: We have treated a variety of conditions, which include basal cell carcinoma, psoriasis, and actinic keratoses, and in all cases the Levulan was applied to the lesional skin. The only time it was applied to perilesional skin was in the ALA-016 study, which we do have slides of, but that is photodamaged skin.

There are anecdotal reports, and our investigators have done studies which are not done as a sponsor phase GCP study, and I can tell you that if you apply Levulan to normal skin, let's say on the arm, a non-sun-exposed area of skin -- and, again, this is anecdotal, I don't have a clinical trial to show you -- the length of time it takes to become photosensitized far exceeds that of the lesion, including actinic keratosis lesions.

DR. DRAKE: Do you have a follow-up comment?

There's a mike back there that's a standing mike or this hand-held mike. If I could ask everybody to please be at the mike to speak.

DR. PIACQUADIO: I think the fundamental issue to that question is really one of safety, and I think the one compelling fact with the treatment here is, although we didn't do any comparative studies with 5-FU or cryo, with respect to healing course in these patients, they healed much more readily than 5-FU for sure, cryo maybe -- it's a little hard to tell -- but absolutely banally. I mean, these people don't have pigmentary or textural changes, at least within the 1,400 or so lesions that were treated in this study.

DR. STERN: I was going to leave this question for later, but since you brought up this issue, I think one issue to me is, if you ask me how much cryo does it take to get rid of an actinic keratosis so it will look good in 8 or 12 weeks, that's very different than how much cryo does it take to have a high probability of this lesion not returning within a year or two, and I'm wondering, do you have any plans specifically or has this cohort been followed with

respect to recurrences over what I would consider a clinically relevant period of time? Making AKs better for 3 months is not a clinically relevant period of time.

DR. MARCUS: There are published reports using other studies that AKs after a single treatment do not recur for a period of at least a year. What we have agreed to with the agency is to conduct a postmarketing study in patients, following them for 1 year to look for recurrence.

DR. DRAKE: I want to be careful we don't get too much off into discussion here, because I think the FDA will address -- remember, the FDA has deemed this efficacious, so efficacy is not an issue before us today.

Jon?

DR. WILKIN: I just wanted to mention a possible asymmetry. Dr. Marcus mentioned some anecdotal sorts of studies on normal skin, and I don't recall that being submitted with the NDA.

DR. MARCUS: No, they were truly anecdotal, and I did not use the word "published."

DR. WILKIN: But basically what we do is, at the FDA, strictly speaking, we don't review drugs, we review information about drugs, and we review the information that has been submitted by the sponsor. So if you're going to bring information up here that we haven't had a chance to review, I think it's important that you identify whether we've had a chance to review it or not.

DR. MARCUS: Point well taken. Thank you, Dr. Wilkin.

DR. DRAKE: Dr. Jordon, and then Joe.

DR. JORDON: Just one clarification so that I'm sure I understand. What's the time sequence between application and the phototherapy?

DR. PIACQUADIO: Per the protocol, it was defined as 14 to 18 hours.

DR. JORDON: Fourteen to 18 hours. Thank you.

DR. DRAKE: Dr. McGuire?

DR. McGUIRE: I had a little trouble with the data, but that's my problem, I think, not the presenter's. How do you score lesions that disappear 75

percent or appear to be nearly gone?

DR. PIACQUADIO: Well, again, I probably didn't make that clear. That criterion refers to the fact that 75 percent or more of the lesions completely cleared. So if the individual had four lesions, for them to meet that criteria, three or more of their lesions were completely resolved.

DR. McGUIRE: I'm glad you clarified that.

DR. PIACQUADIO: Sorry if that wasn't clear.

DR. McGUIRE: That makes it look a little different. Did you then further explore these lesions to see if there were histologic differences between the responders and the non-responders?

DR. PIACQUADIO: Again, in this pivotal trial design, biopsy evaluation was not performed. The only thing that was done is, those lesions, be they treated with vehicle or active, at the 8-week time point were retreated if they still persisted on a lesion-by-lesion basis.

DR. McGUIRE: You did very extensive and very careful dosage studies on concentrations of ALA. Did you similarly perform time duration studies, or did you

pick 1,000 as a good number?

DR. PIACQUADIO: Well, again, I'll probably defer to Dr. Marcus.

Do you want to answer the dose ranging question?

DR. MARCUS: I didn't hear the full question. You said 1,000, being 1,000 seconds of --

DR. McGUIRE: The question was, you did very careful dosage studies with ALA, but then told us that you exposed the patients for 1,000 seconds, and I wondered if 1,000 was arrived at after some clinical experience.

DR. MARCUS: Oh, yes, that was a result of the two light dose ranging studies that you saw, and 1,000 seconds at 10 milliwatts per square centimeter was equal to 10 joules per square centimeter, which is the optimal light dose that you saw.

DR. DRAKE: Okay. I jotted down the hands as I saw them go up, so the next hand I saw was Dr. Mindel. I think I've got all of you down, so we'll get to everybody here.

DR. MINDEL: The inclusion criteria for Grade

A was palpation as well as vision, but the success was vision only, that it looked clearer. I'm just wondering why there was no palpation for complete clearing as well as visual.

DR. MARCUS: I'll defer to Dr. Piacquadio on that.

DR. DRAKE: Dr. Piacquadio, would you mind standing up so that everybody can see and hear you?

DR. PIACQUADIO: Sure.

DR. DRAKE: Thank you.

DR. PIACQUADIO: The question was, with respect to the Grade 1 lesions, the success criteria per protocol, he's saying, basically only had a visual element to its evaluation rather than a visual or palpable element. I must confess, I don't remember that section to that level of detail in the protocol without looking. I can tell you as an investigator performing those trials and as a dermatologist, I think all of them were both tactically and visually evaluated.

DR. MARCUS: I can speak to the Phase III protocol, and the protocol requirements for a complete clearing were both visual and tactile complete clearing,

the design of the protocol.

DR. PIACQUADIO: In fact, we actually used 2x head loops to evaluate these patients, but that's just me.

DR. DRAKE: I'm going to interrupt my list here with the FDA.

Dr. Okun, I think you have a question?

DR. OKUN: Yes. Actually, I can help you, in that I happen to have that information, in that a clearing in the Phase III protocols actually was that adherent scaling plaques would no longer be evident on treated skin when palpated. So there was both visible and palpation as part of the efficacy endpoint.

DR. DRAKE: Thank you.

Dr. DiGiovanna?

DR. DiGIOVANNA: Actually, I had two questions. The Levulan is applied topically, preferably, let's say, in an afternoon. The patient is told to not wash that area and to return the next day, when it's washed off with water. I assume that means that it is able to be moved around throughout that period of 14, 16 hours. What is to keep it from being

moved by the hand into the eye, rubbed on a pillow during sleeping? Because most of these will be overnight. Has that been a problem with photosensitization, or is that something that would be envisioned?

DR. MARCUS: That's a very good question. There have been no problems with photosensitization of any adjacent areas such as you might expect from rubbing or smearing, and in the actual application, because of the hydroalcoholic nature of the solution, the drying is very rapid and virtually complete.

DR. DiGIOVANNA: The second part of my question is that the increase in efficacy at 12 weeks over 8 weeks, is that because of the second treatment at 8 weeks, or was that also seen in some of the lesions that were not treated again?

DR. MARCUS: Any lesions that did not respond at 8 weeks were retreated.

DR. DiGIOVANNA: Thank you.

DR. DRAKE: Dr. Stern was next.

DR. STERN: Yes. In terms of clarification of the subset analysis, I notice that as is in clinical

practice, success rates -- at least in my experience -- on the scalp were substantially lower than they were on the face. I also noted that Type 2 lesions were substantially less successful than Type 1 lesions with respect to clearance.

My question is, what about Type 2 lesions on the scalp? I know it's small numbers, but I have a concern because in some ways those are the most clinically relevant lesions, if you look at what some people would believe are lesions that are more likely to be troublesome in the future. How good is the efficacy there, since scalp in general didn't do terrific compared to the face?

DR. MARCUS: Indeed, the Type 2 lesions on the scalp, interesting enough -- I have a backup slide, but I wonder if, in the interest of time, I could just defer your question, because I believe -- and I don't know if it's good to ask, or traditional, but I believe Dr. Okun is going to address this in his presentation.

DR. DRAKE: Is that correct, Dr. Okun?

DR. OKUN: Yes.

DR. DRAKE: Then that would be fine.

Dr. Abel?

DR. ABEL: My question was exactly the same as that of Dr. Mindel's regarding the palpation of the lesions, because I think that's very important. Photographs don't capture these early AKs that are not all visible, but palpable.

And going back to the definition of defining a complete response, on page 87, I wonder if that could be clarified. It says, "As a complete response, it was designated as a complete response only if the lesion had completely cleared and if adherent scaling plaques of AKs were no longer evident on the surface of treated skin when palpated." That's a little confusing.

DR. MARCUS: I'll defer to Dr. Piacquadio.

DR. PIACQUADIO: Well, again, the question is this term "complete response." Admittedly, it is confusing in the protocol, because the term is used in reference to the outcome or reaction of an individual lesion, as well as these two criterion that are applied at 75 percent and 100 percent. So complete response on an individual lesion is analogous to being completely cleared or gone. When complete response is used for the

global criteria, which apply to all the lesions treated in an individual, four to 15, I think that's where the confusion comes in. It depends on what criteria you're applying, the 75 percent or the 100 percent.

DR. ABEL: I'm talking about an individual lesion. Is it palpable, or is it not? Is there scale, or is there not?

DR. PIACQUADIO: If the lesion resolved, it is both clinically not evident visually as well as palpably.

DR. ABEL: All right. Just one comment as to the comparison between 5-FU. A statement was made that these patients heal faster than with 5-FU, but I think that's very difficult to compare, because we all know that 5-FU is applied to the general involved skin area, whereas these are spot treated.

DR. PIACQUADIO: That's a very valid assessment. There are some people, at least in Southern California, that do spot treat with 5-FU, as amazing as that seems, but I think that is a valid point.

DR. DRAKE: Dr. Lavin?

DR. LAVIN: I was interested in hearing what

the distribution of the lesion severity was for the face and on the scalp, roughly if you knew what that was at baseline for the pivotals.

DR. MARCUS: That, again, is going to be covered by Dr. Okun in his discussion.

DR. DRAKE: Dr. Miller, you're next.

DR. MILLER: This is just a point of clarification.

Dr. Piacquadio, how important is it when you break these ampules for the mixture to be truly mixed? You said you only have to shake it for 2 to 3 minutes, and that's a very long shake if indeed you do have to do this for 2 to 3 minutes, if you're timing yourself. Did you just say that as an aside, or must you do that?

DR. PIACQUADIO: Well, I may ask Sam or Allyn to comment on that. It was set up that way in the protocol, and when you do a trial, you do it per protocol.

Would you like to comment on that, Allyn?

DR. GOLUB: During development, studies were done measuring the dissolution rate and the amount applied following 1 to 3 minutes of shaking. There were

no real differences between those. We've recommended 3 minutes just to make sure that all the contents are completely mixed. We think that 3 minutes is the right number to use, but if a little less than 3 minutes happens to be used, we don't think there will be significant differences.

DR. DRAKE: Ms. Cohen?

MS. COHEN: If I understand correctly, this drug has already been approved? So anything we ask is really already a fait accompli and it doesn't make any difference?

DR. WILKIN: No.

(Laughter.)

MS. COHEN: I needed clarification. Thank you.

DR. DRAKE: I may have misspoken. If we look at the questions that were laid out in front of us, the FDA made a statement that in the data that's been presented to the FDA that they've evaluated, I think -- and it's quoting here -- it says it appears from the data presented that this is efficacious. So I may have misspoken.

Dr. Wilkin, if I did, I apologize. Please help clarify.

DR. WILKIN: Well, actually, we've gotten to the point where we would describe it as approvable.

DR. DRAKE: Okay.

DR. WILKIN: But approval has not occurred yet.

MS. COHEN: Well, I have some pragmatic questions, to begin with. Apparently this has to be applied by a professional. Is that correct? So the patient does not get a prescription, but has to go to a dermatologist in order to get that applied, and then they have to return again.

DR. MARCUS: For the treatment.

MS. COHEN: For the treatment.

DR. MARCUS: The patient can have the diagnosis of AKs done and the treatment, the application, at the same time.

MS. COHEN: Well, there are some practical things, in my mind, in terms of people who have to work, in terms of people who might not have enough money to do some of these things, so it might be a little more

difficult.

But I'm also looking at that nothing was done on fertility studies, there have been no animal studies. There are a lot of things that I see here that have not been done yet. So I'm a little confused as to it's approvable, so I guess if it's approvable, I better not ask these questions.

DR. MARCUS: I would be very happy to respond to your questions, but I will say to you that the agency has issued an approvable letter to the company stating no issues such as those you've mentioned as to be required for approval.

I will tell you that, in the interest of your comfort perhaps, there is a human model for overdosing of this drug for a lifetime, called porphyria, in which patients -- and Dr. Lim or Dr. Poh-Fitzpatrick on our group can speak to that. These patients live their entire life overproducing both protoporphyrin-9 or ALA. We have followed a cohort of these patients by a retrospective data collection for over 20 or 30 years of their medical history, and we have looked to them for signs of birth defects and of excessive development of

any cancers, and what we have found is that the incidence of neoplasms or of birth defects does not exceed that of the general population, and indeed we have submitted this data to the FDA as a human toxicology model.

Dr. Lim, would you care to comment?

MS. COHEN: Now, the other question I have is, a lot depends upon discipline of the patient, that they keep covered, they don't expose themselves. What about people who live in very sunny places, like Arizona or Florida, where there's a lot of sun out there? What happens?

DR. MARCUS: Dr. Piacquadio lives in sunny California. I think he could speak to that.

DR. PIACQUADIO: Yes, I think that's a very valid question. I can tell you at least patients in our trial did not have a problem with that particular issue, and even though it's a valid concern, it doesn't seem to be one in practice that is of importance.

DR. DRAKE: Okay. I want to try to move on to the FDA presentation, unless it's a very important one on clarification, because we're drifting strongly

toward discussion again.

All right. I would like to ask the FDA, then, for their presentation, and I want to thank the sponsor, and don't leave. During the discussion, we may have more questions for you.

Let's now turn it over to -- Brenda Vaughan, are you starting out? I'm sorry. I'm looking at the wrong page. I'm not confused. We've only been doing this for 2 days.

Dr. Okun, would you please start? Thank you.

DR. OKUN: Yes, please.

DR. DRAKE: Brenda, I bet I gave you some excitement for a moment, didn't I?

(Laughter.)

DR. OKUN: If it's agreeable, I'd like to avoid repeating in my presentation the material that representatives of DUSA have already presented in detail. So I will skip over some of these slides very rapidly to avoid repetition.

Next slide.

As already mentioned, the indication is treatment of actinic keratoses of the face and scalp,

and what's novel here is that this is the first drug/device designed to spot treat discrete actinic keratoses.

Next slide.

Dr. Marcus has already covered the proposed mechanism of action, so I think I'll skip this slide and the one subsequent to it.

Skip this one, too, please.

Sponsor evaluated the pharmacokinetics of Levulan-induced fluorescence in actinic keratoses and adjacent skin in 12 subjects. This graph depicts the change in fluorescence over time, with the solid triangles being the fluorescence of the actinic keratosis lesions, and the open triangles that of adjacent skin. What's clear from this graph is that there's little selectivity between Levulan application to actinic keratoses versus adjacent skin sites. Peak intensity of fluorescence is reached at about 12 hours, with a half-life of approximately 30 hours. Fluorescence decreases to about a third of the peak intensity by about 40 hours after application.

Next slide.

Dr. Piacquadio has already discussed a lot of the details of the Phase III protocols. There were two independent Phase III trials, ALA-018 and ALA-019, that had identical clinical protocols performed to support this NDA, and to reiterate just a few of the salient features of the enrollment criteria, four to 15 non-hyperkeratotic actinic keratoses on either the face or scalp to be enrolled. Very thick and/or hyperkeratotic actinic keratoses were excluded from being target lesions. Subjects were men and non-pregnant women over the age of 18.

Next slide.

Baseline Visit A, the Levulan or vehicle was applied to discrete lesions -- spot treatment -- by investigators. The instructions in the protocol to the patients were to avoid direct exposure of target sites to sunlight or other high-intensity light sources, including tanning light devices, to wear appropriate light-protective clothing, and not to wash target lesions.

Now our devices reviewer, Mr. Felten, is going to present just a few overheads of the device.

MR. FELTEN: I don't really think I need to. I think the company has adequately shown you the pictures of what the device looks like.

One comment I will add, though, is that the company has done a very good job in providing us the safety data we would require for such devices in terms of the stability of the output and also the light safety in terms of both the blue light and the UV, and we actually think they've done an excellent job with the device descriptions.

DR. DRAKE: That's a fantastic presentation.

(Laughter.)

DR. OKUN: Next slide, please.

Approximately 14 to 18 hours after application of the drug, 10 joules of blue light with a wavelength maximal of 417, plus or minus 5 nanometers, at 10 milliwatts per centimeter squared was administered to the face or scalp using the device you've seen. In follow-up visits, patients came back 24 hours after light exposure at and Weeks 1, 4, 8, and 12. Unblinded investigators assessed patients for occurrence and severity of adverse events.

Because it was anticipated the occurrence of adverse events would unmask allocation to treatment -- next slide -- blinded investigators did the efficacy assessments at Weeks 4, 8, and 12, and as already mentioned, patients with persistent target lesions at Week 8 were eligible for retreatment. The primary efficacy endpoints did not use patient assessment, investigator assessment, and I should mention parenthetically, since there was some discussion about comparisons between 5-fluorouracil and ALA, that in this study there were no prospective comparisons of either efficacy or tolerability. The information that was presented was patients' recollections of their experience with past treatments of their actinic keratoses.

Efficacy endpoints, the primary was at Week 8, follow-up was at Week 12, which included patients whose target lesions were retreated at Week 8.

Next slide.

If this issue hasn't been clarified yet, hopefully we can clarify it here, that the primary efficacy variable was 100 percent complete response rate

in our analysis, which was the percentage of patients with all target lesions cleared, and the definition in the protocol, adherent scaling plaques no longer evident on treated skin surface when palpated. This was considered a satisfactory endpoint, because Levulan was designed to treat discrete lesions rather than areas of skin.

Other efficacy variables considered were the 75 percent complete response rate, which is percentage of patients with 75 percent more of their actinic keratosis target lesions cleared, and the lesion response rate, which was the percentage of target lesions cleared.

Now I'm going to ask our statistics reviewer to discuss some of the efficacy results.

MS. FARR: Thank you.

My name is Shahla Farr. I'm the biostatistical reviewer for this NDA. Today I will be presenting the efficacy aspects of Levulan solution, except now I will be presenting them in each individual study separately.

The sponsor has submitted two identically

designed multicenter, investigator-blinded, randomized, unbalanced parallel group, vehicle- and blue-light-controlled pivotal studies in patients with multiple actinic keratoses of the face and scalp. This table lists the two pivotal trials. Eight centers in the United States participated in each of these studies. After qualifying for the study, subjects were randomized in a 3:1 ratio to receive either Levulan or vehicle applicators, respectively.

In our review, the primary endpoint parameter was based on the percent of subjects who were completely cleared of all their targeted lesions at Week 8, based on an intent-to-treat population. At Week 8 if an observation was missing, it was considered a failure. In addition to the per-subject analysis, a per-lesion evaluation was performed. These analyses were done based on per-protocol instead of intent-to-treat.

In order for this drug product to prove efficacy, the sponsor has to demonstrate the superiority of Levulan solution to its vehicle in each of these two studies separately. I will be referring to these studies as Study 018 and 019 throughout this

presentation.

Next slide, please.

Study 018, a total of 117 subjects from eight centers were enrolled into Study 018, where 88 subjects were randomized into the Levulan and 29 into the vehicle arm. No statistical differences were found between the two treatment arms in regard to the demographics and baseline characteristics of the subjects.

And to answer your question, Dr. Lavin, that's showing the distribution of lesions or subjects for face and scalp separately. I think that was one of your questions.

DR. LAVIN: I asked within face and scalp, not overall.

MS. FARR: Next slide, please.

This table summarizes the results of the analysis for the primary endpoint variable, which was the percentage of subjects who had 100 percent of their lesions cleared. As is seen in this table, highly significant results were observed when Levulan was compared to the vehicle arm relative to the rate of complete clearance.

Next slide, please.

This table summarizes the results of the analysis for the primary endpoint variable for subjects who had 75 percent or more of their lesions cleared, and as you can see in this table, highly significant results were observed when Levulan was compared to the vehicle arm.

Next slide, please.

This is Study 019. A total of 126 subjects from eight centers were enrolled into Study 019, where 90 subjects were randomized into the Levulan and 33 into the vehicle arm. No statistical differences were found between the two treatment arms in regard to the demographics and baseline characteristics of these subjects.

Next slide.

This table summarizes the results of the analysis for the primary endpoint variables for subjects who had 100 percent of their lesions cleared for Study 019. As is shown in this table, highly significant results were observed when Levulan was compared to the vehicle arm relative to the complete clearance.

Next slide, please.

This table shows the result of the analysis for subjects who had 75 percent or more of their lesions cleared for Study 019. Again, as we can see, highly significant results were observed when the two arms were compared to each other.

Next slide, please.

Now, as I mentioned previously, the lesion analyses were based on per-protocol. Now I'm looking at the total number of lesions of the patients. This is Study 018. A total of 803 lesions were under the study. Of these, the data was available for only 784 at Week 8. This table gives the response rate for these lesions. Highly significant results were observed when Levulan was compared to the vehicle arm.

Next slide, please. Thank you.

Now the lesion analysis for Study 019. A total of 1,086 lesions were under the study, and of those, the data was available for 1,066 at Week 8. This table gives the rate of response for these lesions, and, again, as we can see, highly significant results were observed when Levulan was compared to the vehicle arm.

Next slide, please.

Now, this is the subset analysis. The two data sets were merged, and subset analysis was done based on lesion counts by gender, age category, which was younger than 60 or 60 and older, skin type, and the location of the lesions, which was face or scalp. Highly significant results were observed in each one of these subcategories.

Next slide, please.

Conclusions. The results of the analysis of efficacy of the two studies, Study 018 and 019, demonstrate that Levulan Kerastick topical solution, 20 percent, is statistically significantly better than vehicle in the treatment of multiple actinic keratosis of the face and scalp.

Now Dr. Okun will continue this presentation.

DR. OKUN: This slide shows a flow chart reflecting the patient outcomes from pooled pivotal trials. It's a little complicated to look at. We'll just take a few minutes to go over it, because there is actually a great deal of information here.

Firstly, I should mention that the outcomes

from the pivotal trials were pooled in this flow chart merely for illustrative purposes. This approach is justifiable because the two trials had identical protocols, and it's worth noting that the results from the two trials were not pooled in the review process. Each trial standing on its own achieved clinical and statistical significance.

DR. DRAKE: Excuse me. Could I ask you to bring the mike a little closer?

DR. OKUN: I apologize. I'll try and be more conscious of that.

Only two patients in the active treatment arm were discontinued due to adverse events experienced during light treatment. Five others in the active treatment arm and three in the vehicle arm were lost to follow-up.

A couple of points suggest themselves from this slide. First of all, clearly the majority of patients who were treated with Levulan experienced 100 percent complete response by Week 8. You have 180 being treated here, and at Week 8 117 are counted as clear, 60 as not clear, with a couple dropping off, to explain how

the numbers add up. Most of those who were clear at Week 8 remained clear at Week 12. Of those retreated at Week 8, which is over here, about half had 100 percent complete response by Week 12, going from here to there. And when you look in the vehicle arm, obviously, of those treated at Week 0, an extremely small number were 100 percent completely cleared by Week 8.

Next slide.

This slide shows a table recapitulating the 100 percent complete response rate of the pooled pivotal trials, looking not only at all patients, but also the subset analysis, the patients with face and with scalp lesions, both at Week 8, as over here, and at follow-up at Week 12.

Several conclusions suggest themselves from this table. Firstly, that active treatment is superior to vehicle. Retreatment at Week 8 improves overall efficacy, going from 65 percent to 69 percent, and the recurrence of scalp lesions between Week 8 and Week 12 reduces the scalp subset efficacy when you're comparing across those two time periods. Finally, across both time periods, outcomes for patients with face lesions

were superior to outcomes for patients with scalp lesions. A possible reason why patients with face lesions fare better is suggested in the following slides.

Next slide.

This slide shows the lesion response rate at Week 8 from the pooled pivotal trials, looking across different lesion grades, where Lesion Grade 1 are the thinner lesions and Lesion Grade 2 are the thicker ones. What you can see is that the lesion response rate is better comparing Levulan versus vehicle, and also somewhat better for thinner lesions compared to thicker lesions. One possible explanation for this might be that percutaneous penetration of Levulan may be superior in thinner lesions, thus making treatment more effective in that subset.

Next slide.

In comparing the distribution of lesion grades in the different sites at baseline, it's clear that the majority of face lesions are thinner, while the majority of scalp lesions are thicker. Since, as the previous slide showed, thinner lesions respond better to

treatment, it may be that the higher proportion of thinner lesions on the face explains the greater efficacy for patients with face lesions.

Next slide.

In assessing safety, 232 patients, which includes patients enrolled both in Phase II and Phase III studies, with Fitzpatrick skin types ranging from I through IV were treated with Levulan 20 percent solution and between 6 and 10.9 joules per centimeter squared blue light. There were additional patients in the Phase II studies, but there were 232 who were treated under these conditions. There were no deaths, serious or systemic adverse events attributed to treatment which emerged during the clinical trials. Transient local cutaneous adverse events occurred in most patients.

Next slide.

This slide shows the incidence of adverse events in the period between drug application and light treatment, and it shows the fraction of patients who reported any sign or symptom. Patients treated with Levulan, about 44 percent reported burning and stinging at some time point between drug application and light

treatment, compared to 10 percent of control, and about 13 percent active treatments had edema. It is possible that these symptoms result from inadvertent exposure of the target lesions to ambient light in the time period between drug application and device activation, perhaps thereby initiating a low-grade photodynamic response. The alternate possibility is that the Levulan itself is directly a dermal irritant.

Next slide.

This slide shows, in the time period during and/or 24 hours after light treatment, the fraction of patients who report burning, stinging, or edema at any time in that interval. One hundred percent of the Levulan-treated patients reported at least some degree of burning or stinging in this time period, compared to about 50 percent of the controls, and 48 percent of Levulan patients had edema on at least some of their target lesions, compared to 0 vehicle.

Next slide.

Fifty-seven percent of the patients characterized the burning and stinging as severe at least at one time point during this time interval. Dr.

Piacquadio's point is well taken that for the vast majority of patients who reported severe burning or stinging at one of those time points, they did not necessarily have severe burning and stinging during the entire time period. This is just the percentage of patients who reported that at least once during that time interval. The edema and burning/stinging usually resolved within 24 hours after light treatment, and more than 90 percent of the patients eligible for retreatment at Week 8 were willing to undergo retreatment.

Next slide.

This slide shows adverse events noted longer than 24 hours after light treatment. Specifically discussing the adverse events that developed in more than 5 percent of patients, the most common adverse event is scaling, crusting, scabbing as these lesions resolve.

I'd like to make special mention of the prevalence of -- rather, the incidence of hypo- and hyperpigmentation, which was 27 percent in Levulan and in vehicle. What this number refers to is the percentage of patients who developed hypo- or

hyperpigmentation on at least one target lesion during follow-up after treatment. This analysis is a little different from the sponsor's analysis, because they were looking at the per-lesion likelihood of hypo- or hyperpigmentation, and this refers to the per-patient likelihood of developing hypo- or hyperpigmentation on at least one target lesion.

Other adverse events experienced include itching, more common in Levulan than vehicle, erosions, wheal/flare, and other non-specified skin disorders.

Next slide.

Adverse events reported by a smaller percentage of patients included pain/tenderness, ulceration, bleeding, vesiculation, pustules, and dysesthesia, and these are all more common in Levulan-treated than in vehicle-treated patients.

Next slide.

Most local cutaneous adverse events were mild to moderate in intensity and short-lived. The few patients who developed ulcers on these sites, the ulcers healed without evidence of scarring.

Next slide.

Laboratory evaluations were, no clinically significant laboratory abnormalities following treatment. Two percent of Levulan-treated versus no vehicle-treated patients had normal baseline urine ALA levels that became marginally elevated after treatment. This information should be considered in the context that these marginally elevated post-treatment urine ALA levels were lower than the baseline urine ALA levels of three of the study participants.

Next slide.

In conclusion, the Levulan Kerastick topical solution, 20 percent, and blue light treatment effectively treats non-hyperkeratotic actinic keratoses of the face and scalp. Adverse events associated with treatment are local, cutaneous, not serious, generally mild to moderate in intensity, and short-lived.

DR. DRAKE: Thank you.

All right. We've now reached the point of the afternoon where we're now going to open the discussion to the committee.

Dr. Wilkin, do you have any sort of instructions for us? We have the questions you've posed

before us, and would you mind reviewing those so we make sure we try to give you the information that the agency needs?

DR. WILKIN: Yes.

DR. DRAKE: Excuse me. Just one second.

Henry?

DR. LIM: I have a question of clarification.

DR. DRAKE: Yes?

DR. LIM: Specifically on the device issue --

DR. DRAKE: I'm sorry, I should have asked for that. I apologize. You're absolutely right. That should come before we go to Dr. Wilkin.

Jon, will you pardon me for just a moment while I do what I'm supposed to do here?

Yes, Dr. Lim?

DR. LIM: Specifically on the device issue, I'd like to congratulate the sponsor for developing a very interesting light source with a very reputable light source manufacturer, which is National Biologics.

I do have a question about how to monitor the output of this light source. This light source has a peak at 417. Most of the photometers that are in the

regular phototherapy clinic are not going to be able to measure this, and I don't see in the picture that was provided an internal meter that comes with it. So what is the recommended maintenance, and how do we know the half-life essentially of these light bulbs?

MR. FELTEN: The phosphor that is used in the bulb is specifically designed to put out that wavelength at 417 nanometers. The company has done lifetime studies showing that the life of the bulb, if I remember correctly, goes out as long as 328 treatment cycles, which is long, long treatment cycles, and your question that will be addressed in one of our questions back to them will be about wavelength, about how to track the life of the bulb, and it will probably be based, on our recommendation, on some type of cycles of treatment, because all the treatment cycles are exactly the same, which would be 1,000 seconds. So we would just limit them by how many treatments they could recommend before the bulb should be changed.

But the phosphor is designed specifically for that wavelength and that output. And they have looked also at the stability of these bulbs, and they're stable

during these treatment cycles for at least an hour, maintaining the output level both in wavelength and in energy. So that has been tested.

DR. LIM: Thank you.

DR. DRAKE: For 1 hour, did you say?

MR. FELTEN: The testing shows that over an hour period of time, the bulb stays steady for wavelength and energy, which is --

DR. DRAKE: Over the period of an hour.

MR. FELTEN: Almost four times longer than the treatment cycle.

DR. DRAKE: Right.

MR. FELTEN: And then what they did is, they did a series of on/off cycles where the bulbs were run, the thing was rested, turned back on, out to over 400 cycles, and all of the machines that they looked at have at least 300-plus cycles before the bulb started to show deterioration. So we will limit their lifetime based on that kind of --

DR. DRAKE: On the number of cycles.

MR. FELTEN: Right.

DR. DRAKE: Got you. That's interesting.

Okay. I have Dr. Kilpatrick, and then Dr. DiGiovanna.

DR. KILPATRICK: Ms. Farr made a comment which intrigued me. She said that in the subjects randomized to treatment, all targeted lesions were treated, which implies, being legalistic, that some lesions were not treated?

MS. FARR: Well, they were supposed to choose -- patients who were entered to the study had between four to 15 lesions. These were the targeted lesions. So they were treating these lesions -- for example, a subject might have had four lesions, another subject might have had 10. So for all these subjects that they had chosen, all these targeted lesions had been treated, and success was --

DR. KILPATRICK: I understand. I understand.

MS. FARR: Go ahead.

DR. KILPATRICK: But your answer is no, there were no untreated lesions in individuals who were selected for treatment by randomization.

DR. DRAKE: Dr. Okun?

MR. FELTEN: Dr. Okun?

DR. OKUN: In fact, there were untreated lesions in the patients who were selected for randomization. For example, hyperkeratotic lesions were --

DR. KILPATRICK: Yes, of course.

DR. OKUN: Not supposed to be treated. It's possible in this protocol for patients, for instance, to have more than 15 lesions, and they would have no more than 15 of those treated.

DR. DRAKE: Okay. Dr. DiGiovanna?

DR. KILPATRICK: May I pursue this, please?

DR. DRAKE: I'm sorry, Dr. Kilpatrick.

DR. KILPATRICK: And may I be a little bit pedantic?

DR. DRAKE: Yes, sir.

DR. KILPATRICK: Donald Minland published a text called "Elementary Medical Statistics" back in the 1960s, in which he makes a big distinction between sampling units and measurement units, and sampling units are those units that are randomized -- here in this case, subjects -- measurement units in this case would be the lesions, and you, I think, very properly have

focused on the subject analysis per subject, but subsequent to that we get into lesion analysis, and then analysis by different lesion grades. And while I'm being pedantic, I don't think it makes any difference, but there are other possible explanations for differences between lesion grades in terms of Phil's point about the distribution of different lesion grades in different patients.

So I'm just being pedantic. I don't think it's a big issue. Thank you.

Thank you, Madam Chair.

DR. DRAKE: You're very welcome.

Dr. McGuire? I'm sorry. Now Dr. DiGiovanna.

DR. DiGIOVANNA: I'm not certain I'm at the right point to ask this, because I'm not certain it's a point of clarification, but I think that this is probably about as good --

DR. DRAKE: That's okay. We've started moving on anyway. Go ahead.

DR. DiGIOVANNA: This is a junctional sort of question, and you might be able to clarify this quickly. But what focused me on it was the last part of the

FDA's presentation that the adverse events associated with this were not serious, mild to moderate in intensity, and short-lived. My understanding of this compound, from what I have in the literature that was given to us, is that it does cause oxidative damage to DNA. My understanding is that what we are doing here is attempting to treat premalignant lesions in a way that to a large extent partially treats those lesions.

We've learned a lot about skin carcinogenesis over the last 5 to 10 years, enough to know that there are specific mutations that have been identified in skin cancers and in precancers, and that the accumulation of those mutations are very clearly associated with the development of malignancy, and the concern that I would have here is that if one is taking a large number of premalignant lesions and exposing those lesions to agents that damage DNA and are not totally eradicating those lesions, then the adverse event that I would be interested in is the long-term development of malignancy in the areas that have been treated.

And if I'm not correct that that should be what I'm concerned about, can you explain to me why?

And if I am correct, then what sort of studies would be done to follow, to monitor for that outcome in these individuals who are at a high risk?

DR. DRAKE: I would ask Dr. Okun, and also, even though the company has completed your presentation, from time to time I may ask if you have something pertinent to add to that.

So, Dr. Okun, may you address that question first?

DR. OKUN: Well, I think answering that question requires a thoughtful response.

You know, I understand your concerns, Dr. DiGiovanna. First of all, just to clarify, in the conclusions we said that the adverse effects are short-lived, and it perhaps would be more precise to say the adverse events that were observed were short-lived. As was discussed in the protocol outline, patients were not followed for a period longer than 3 months. A period in which in humans carcinogenicity would be observed would be considerably longer than that time period. So in fact at this juncture, based on what has been submitted from the studies for this NDA, there is follow-up for no

longer than the conclusion of those 3 months.

The issues that you raised that are potentially of concern would, I suppose, need to be addressed in terms of having longer-term follow-up on patients who are being treated with this modality to test the hypothesis about whether they are having a higher rate of carcinogenic progression.

Now, again, one consideration in this sort of study design is, obviously, we're dealing with a study population where there is already underlying risk of skin carcinogenesis, given the enrollment criteria by which they're enrolled. So special attention needs to be paid in terms of study design to think about how one would be able to separate a theoretical or potential signal from the ALA as opposed to the endogenous signal from these folks because of their pre-existing solar history exposure.

DR. KILPATRICK: Martin, Table G-10 of the adverse events indicates that 3 percent of, I think, the patients had carcinoma of the skin. Again, is it possible that the photodynamic therapy was a causal agent in this?

DR. OKUN: These were cancers that were diagnosed before or during --

DR. KILPATRICK: Okay. Thank you.

DR. DRAKE: Dr. Lim, I think you might have a comment on this issue.

DR. LIM: Yes, just to try to address Dr. DiGiovanna's questions. I think one can look at it on two levels. One is that the mechanism of action of this topical ALA is through the generation of protoporphyrin, which, upon exposure to the active spectrum, which is a solar band, it would go the exitus state, the exitus state would interact with the oxygen molecule to form the singlet oxygen. The site of action primarily is in the cell membrane, so it would cause lysis of the cell. I don't think we can completely answer the question and the concern that you raised, specifically DNA damage. It primarily is on the cell membrane. That is number one.

Number two is that the other therapies for -- the 5-FU specifically, I'm not sure if you know it doesn't damage DNA either.

And then, thirdly, as was mentioned before,

there is a very large cohort of patients with erythropoietic protoporphyria, which is an experiment in nature where they have tremendously elevated levels of protoporphyrin in the skin as well as in the red cell, and to a lesser extent in the plasma, and to my knowledge, there is no report that those patients as a group have a higher incidence of skin cancer. Dr. Poh-Fitzpatrick, who has followed a large group of patients, is in the audience, and I believe she can confirm that.

DR. DiGIOVANNA: Can I just respond to that?

DR. DRAKE: Yes, but I was going to ask Dr. Maureen Poh-Fitzpatrick to comment, too. So, John, go ahead, and then let Maureen have a say.

DR. DiGIOVANNA: You are correct that if you generate enough toxic oxygen species and other toxic agents, that you kill the cell, and I don't have a problem with that. You can do that with cryotherapy, and you can do that with a number of other agents. I have a problem with the inadequate treatment of the premalignant lesion, whereas you kill a percentage of the cells that already have sustained one hit of a two-hit-leads-to-cancer hypothesis, and then the remaining

cells, some have sustained an additional amount of DNA damage.

I did consider the point that you were talking about, that there are a lot of people who are walking around who have had high levels of these compounds for many years; however, they may have the sustained exposure to -- I don't know what the incidence of actinic keratosis in that population is, but it very well may be that those lesions occur at a lower level because they're totally destroyed early on.

I think the concern here is really the partial treatment of lesions. I think if you can destroy the premalignant lesions, you remove the problem. If you partially treat it with an agent that causes DNA damage, you've raised a different scenario, and you've taken someone who has a predisposition to cancer -- for example, an individual analogy would be someone who has a nevoid basal cell carcinoma syndrome, and they have a number of cells -- all of their cells have one hit already, and additional exposure to a DNA-toxic agent will increase their risk.

DR. DRAKE: But, as pointed out, I think one

can make that argument for everything we currently use to treat actinic keratoses.

DR. DiGIOVANNA: I don't think that's true, because cryotherapy doesn't necessarily cause selective DNA damage. It destroys the cells. I mean, if I'm wrong, please tell me, but I think these are --

DR. LIM: I'm not sure about that.

DR. DRAKE: I'm not sure about that, because you're clearly disturbing, perturbing the barrier function, and if these people go out and get more UVA exposure, how do you know you're not subjecting them to additional DNA damage? Because you've perturbed the natural protective barrier that might have been there before you froze them.

DR. DiGIOVANNA: Usually cryotherapy is a timely isolated event, and I don't know of liquid nitrogen being a DNA specifically damaging agent, like reactive oxygen species are.

DR. DRAKE: There are two people who still want to respond to this particular thing.

Joe, yours isn't in response to this, is it?

All right. I'm going to ask Maureen, whom I

already asked, and Rob wants to respond.

So, Dr. Maureen Poh-Fitzpatrick, welcome.

DR. POH-FITZPATRICK: I'm Maureen Poh-Fitzpatrick. I'm professor emerita of dermatology at Columbia University, and clinical professor of dermatology at the University of Tennessee.

I've had the opportunity to follow a cohort of patients with protoporphyria for 20 to 30 years, and in those patients, combined with the data from Dr. Micheline Matthews-Ross from the Harvard Medical School, in about 153 patients with this disease, some of whom are now octogenarians, there were no skin cancers tabulated from our databases and one with actinic keratosis.

Now, whether that means that these people never go out in the sun so, therefore, they're protected, that's a possibility. And the other possibility is that indeed there is some kind of low-grade protective effect from the porphyrin in the skin, although there is absolutely no data to support that at all.

So in point of fact, these people haven't

gotten skin cancers and they haven't gotten actinic keratosis for some reason, and they're certainly not at high risk of having a genetic predisposition through some other gene -- of having a P53 mutation, for instance -- and then having this protoporphyrin alongside over a lifetime doing whatever concurrent damage it may do.

So these are the data that I can sort of throw out to help in the discussion.

DR. DRAKE: Thank you.

And Rob?

DR. STERN: I think if you look at the mechanisms going on here of carcinogenesis and you consider this 1,000-second hit, even if there are cells that do survive and they're DNA damaged, compared to the overall progression of carcinogenesis in actinic keratosis or sun-damaged skin, the biologic insult in terms of the likelihood of leading to cancer is likely to be trivial, on the one hand.

On the other hand, I think the point that John alluded to is, what are the effects of incomplete treatment, and what was disturbing to me was that even

with the non-responders getting a second treatment 4 weeks after the initial prime endpoint, 8 weeks, on the lesions that at least in the people who get them -- elderly men are considered higher-risk lesions in terms of progression to carcinogenesis, all on the basis of clinical data, likelihood of metastasizing -- in fact the clearance rate went down even 4 weeks after the initial time, and these are in selected, pretty thin lesions.

My concern is, is this really ready for prime time with the data we have in terms of scalp lesions? I think the data on face lesions is clear in itself, but I have real doubts about is this really safe and efficacious for scalp lesions if you have recurrences within 4 weeks that outweigh further clearances with an additional therapy.

DR. DRAKE: John, thank you. It's a good question, and where you might want to think about this is in Question 4 in terms of thinking about what studies might be done to continue to answer this very important question you've just asked. I mean, I don't disagree with you in terms of -- we must think about it, if

nothing else just looking at the PUVA data over a long period of time. So it must be thought about.

Dr. McGuire?

DR. McGUIRE: I had a couple of points. One, unless I misunderstand the data, there appears to be no selectivity between normal skin and lesional skin. That is, the duration of fluorescence and the intensity of fluorescence are the same. And I assume that that means that the toxicity in non-lesional skin will be about the same as it is in the actinic keratoses. If I'm wrong about that, I'd like to hear about it.

But the piece of data that is most concerning to me is the one that Dr. Okun said was a little bit busy, and it is busy, but what it tells you is that after 8 weeks of therapy, of the 117 individuals who cleared, 14 have recurred by 12 weeks, and one doesn't know if in another 4 weeks another 10 or 14 would have recurred, and then in another 4 weeks another 10 or 12 would have recurred.

We're dealing with a biological process with a time base of 10, 20, 30 years, and to make a prediction on the basis of a 12-month exposure to a

particular modality seems to me to be -- I don't see how one could come to the conclusion that one is achieving remissions with this therapy, although that may very well be the case, but I think we need a longer window to look at these results.

Thank you.

DR. DRAKE: Dr. Kilpatrick, I had you down. Did you get your question answered? Okay.

Other questions?

(No response.)

DR. DRAKE: I had one.

Dan, I believe it's a slide you showed, the first one. You can't judge very well from pictures, but I can tell you from sitting here, it almost looked like a basal cell to me instead of an actinic keratosis, and maybe it's my glasses, I don't know, but I have a question.

Has the sponsor thought anything at all about superficial basal cells? And you can't change a clinician's diagnostic acumen in this room. I mean, that's not possible. But have there been any studies at all where people went behind it after treatment and did

biopsies to see what was left, what was the residual AK left, was there any tumor that was undetected? Has anybody followed these up with some biopsies post-treatment?

DR. MARCUS: I can respond to that in terms of the efficacy that has been published in the literature. There have been a number of papers on literally hundreds of patients treated for superficial basal cell carcinomas with ALA PDT with various light sources, and some of those studies have indeed used biopsies to assess efficacy. These studies have also used multiple treatment until the lesion had clinically completely disappeared. The biopsy rate of complete response in papers which have been submitted in the NDA, but, again, for basal cell carcinoma, state that they range from about 60 percent to 90 percent complete clinical response based on biopsy-proven efficacy.

But, again, these are published papers, and I can't vouch for the good clinical practice of the studies. However, the question you asked if there were any studies done, indeed there are. I believe this also speaks to the issue of partial treatment, but, again, it

has been postulated as a possible treatment for superficial basal cell carcinomas.

DR. DRAKE: Well, I know that the basal cell data -- I guess I didn't make my question clear. I know about the basal cell data, because Dr. Anderson and crew did that at Mass General when I was there. But have there been follow-up biopsies on the AK studies with your product? I'm sorry. That's what I was trying to ask.

DR. MARCUS: Thank you for clarifying. No, there have not been biopsies on this study.

DR. DRAKE: Okay.

Dr. Abel?

DR. ABEL: I have a question for clarification as to exclusions. Why were the patients on photosensitizing medications excluded? I mean, this certainly represents a large number of the elderly population, and most of these photosensitizing drugs have an action spectrum in the long UVA range, and maybe this extends to the visible light range, too, if someone wants to speak to that. But I think this would be a large part of the population that wouldn't be able to be

treated if photosensitizing drugs are an exclusion.

DR. MARCUS: The exclusion of patients on concomitant photosensitizing medication was done purely for the sake of the purity of the clinical trial design. We did not want to contaminate adverse events or greatly increase the size of the study by stratifying for it. We were also potentially concerned for additive effect. So, indeed, the adverse events you see are the adverse events due to Levulan and not due to Levulan plus any other photosensitizer.

DR. ABEL: That does bring up the issue of safety in this group of patients.

DR. MARCUS: As I say, we wanted to present to the agency and to understand the safety of Levulan, period, and we didn't seem to have trouble accruing patients who were not on photosensitizing drugs with their AKs.

DR. DRAKE: May I just suggest that that's another preemptive strike or suggestion for Question 4. I mean, that's something the agency might even think about. I think it's rather customary to eliminate photosensitizing drugs in the study when you're looking

at a potential photosensitizer. I think that's pretty customary. But that kind of information gets picked up in subsequent studies.

Other questions of clarification before we ask Dr. Wilkin to explain the questions?

(No response.)

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: Well, I would say that the committee's comments have already dealt with 75 percent or more of the questions that we've raised. The first one is relating to the lesions that are hyperkeratotic and how should we craft this into labeling: Should the label restrict the use of this combination drug/device to lesions that are not hyperkeratotic?

The second question is the relevance of the 75 percent or better complete response rate, is that helpful to clinicians and to patients? Would that be useful to craft into the labeling, or would the committee believe that just simply listing the 100 percent complete response rate measure would be sufficient?

And then there is language in the labeling

that speaks to incidental photoexposure outside of the \clinician's office, and you've had a chance to look over the labeling, and do you have any comments that might amplify or modify that in a way that would make it more informative?

And then, finally, are there any additional studies that the committee believes would be helpful?

This is our list of things that we'd like, but if you come up with additional items that you'd like to share with us, we'd appreciate that.

DR. DRAKE: Thank you, Dr. Wilkin.

I think just so we have it very clear on the record, because there may have been members of the committee who have comments to make on the questions, but were holding them because they didn't feel that they were points of clarification, I would like to go through them one by one to make sure every member of the committee has an opportunity to contribute when they want to.

Let's please address Question No. 1: Should the label restrict use of Levulan to lesions that are not hyperkeratotic? And if so, how do you want to

define what's the level of keratosis?

Oh, boy, a lot of hands. Fred, I'm going to call on you first, because I saw your hand first.

DR. MILLER: You know, I think that in the label it should just say that the hyperkeratotic lesions were not tested. But I think practically speaking what's going to happen is people are not going to use this preparation just spotting it on actinic keratoses as they're identified. The patients that we see have significant damage, and many times one actinic keratosis blends into the next one, and if you begin to spot it, when you're finished you're going to have every aspect of the skin completely covered.

DR. DRAKE: Ms. Cohen, I believe I saw your hand next.

MS. COHEN: No, I was just smiling.

DR. DRAKE: You were just smiling. All right.

(Laughter.)

MS. COHEN: I liked what he said, so I smiled.

DR. DRAKE: Rob Stern, I saw your hand, too,

please.

DR. STERN: Well, I guess I feel perhaps differently at least -- and I heard Fred. To me, as I read these data, I think that until there are good data to the contrary, to my mind, there should be an exclusion about or a warning about the lack of proven efficacy both in the scalp and for hyperkeratotic lesions, because I think what I heard from Fred, which is exactly as I'd anticipate, unless there are particular exclusions that are prominent, it's going to be used widely and perhaps with an expectation of efficacy that we have nothing to expect.

And the third part, of course, is in terms of labeling, giving people some idea of what the limitations are in terms of how long these have been followed relative to the natural history of these lesions, and that will perhaps encourage the sponsor to do studies that give us further data that would allow us to modify the label in the future.

DR. DRAKE: Phil?

DR. LAVIN: I would agree with you on the hyperkeratotic lesions, but the data are very compelling

in favor of efficacy for the scalp. When you see 55 percent against 10 percent and 50 percent against 10 percent, whether you do the per-protocol or the intent-to-treat, those are strong, and those P values are real. So I think maybe the only thing that might potentially be dissuading is if the distribution of the type was imbalanced and all of the scalp ones were in the 1 category. That might be the only thing that could dissuade it, but it didn't look like that from any of the data that people were presenting.

DR. STERN: Perhaps I misunderstood it, but what I understood from the statistical presentation of the scalp data, as I recall the numbers, they went down from Week 8, approximately 55 percent response, to Week 12, approximately 48 or 50 percent response. There was about a 5 percent reduction in response, in spite of the fact that all of the non-responsive lesions at Week 8 were treated. So in other words, there were more lesions that reoccurred than there were lesions that responded to additional treatment.

So to me that is prima facia evidence. You know, one has to go on the limited data, but my

interpretation of that data is that if this stuff works on the scalp, it doesn't appear in very many cases to work for very long if you have more reoccurrences in 4 weeks than you have ability to clear with the second treatment, which is quite different than the face, where it went up in percentages. So statistically you're absolutely correct that if you kept on treating people every 4 weeks for every lesion that reoccurred, you would maintain that 50 percent.

DR. LAVIN: That's how I would say it was.

DR. STERN: But to me, as something that's approvable, those data are a pretty compelling argument against approving it on the basis of those small samples.

Am I wrong in how I interpreted those data?

DR. OKUN: Those are the data. That's correct.

DR. DRAKE: Other opinions on scalp? I want to take these two separate. Let's talk about scalp for a minute. Other opinions on scalp?

John?

DR. DiGIOVANNA: The other issue with respect

to scalp is, it may be that the quality of or the severity or the thickness of the lesions was different, but it also may be that the skin is different, in that the scalp, even in those of us who are more sun-exposed on the scalp, does have hair follicles, be they small, and actinic keratoses sometimes involve those hair follicles, and superficially the treatments that work from the outside in may destroy the superficial part of lesions and leave the deeper areas that involve the hair follicles.

So that may be one reason why we would see more recurrences in the scalp rather than on the face. That would not be because the quality of lesions treated were different.

DR. DRAKE: Dr. Kilpatrick, and then I want to -- well, Dr. Kilpatrick, right before you do it, I think Dan has a response to that. Would you --

DR. KILPATRICK: Well, because it may anticipate, I was wondering whether Dr. Stern would accept a compromise situation, where the label indicated that the scalp was not as effectively treated.

DR. STERN: It's not a matter of -- I just

want people to be aware of the limited data we have and where it seems to work better and worse very clearly, not buried in the label, but in an explicit fashion. I certainly don't have any strong feelings about approvability or non-approvability and how to handle that. I'd leave that up to the agency. But I wanted to make my point in terms of from a clinical perspective, to me that's a very important point, and how it's handled is fine.

DR. DRAKE: Okay. And then Ms. Cohen, and then I'm going to ask Dan.

MS. COHEN: If I understand correctly, everybody's going to have to go to a physician, so patients are not going to be seeing the label unless there is a patient insert or a patient information sheet that's handed to them in the doctor's office so they can read what it's about. I think they're entitled to have this information, and if it's only going to be exclusive to the physician, I don't think that's allowing consumers to make an intelligent decision.

DR. DRAKE: Bob, is it related to that?

DR. JORDON: It's related.

DR. DRAKE: Please, Dr. Jordon.

DR. JORDON: I think you need a patient handout of some sort anyway just to describe what kind of protection these patients have to use when they leave the office to come back for their photolight. There really needs to be a separate patient handout that's gone over with the physician when they go through this therapy, or it's going to be very, very difficult to protect these people.

MS. COHEN: You know, the patients who have been seen are seen under the optimum circumstances, where they're going to be constantly reminded they should keep covered, et cetera, et cetera. But in the real world you can give patients instructions, but not necessarily are they going to be fulfilled. So this kind of thing really has to be bulleted so they see it and have it in their hand. I'd even have them sign something saying that they've acknowledged that they are supposed to wear protective covering during this process.

DR. DRAKE: Dan, would you please -- I think the sponsor had a comment.

DR. PIACQUADIO: Yes, I just wanted to make, I guess, one clarification point. I guess we're talking about two key issues here, one a regional therapeutic difference, face versus scalp, and then a therapeutic difference based upon the grade of these lesions, be it Grade 1, Grade 2, or Grade 3.

If we look at the data -- and I just happen to have this table with me -- there is a preponderance of these thicker Grade 2 lesions in the scalp for the aggregate study. There are 166 lesions of Grade 1 versus 180 of Grade 2 on the scalp, versus the face that had 551 Grade 1 lesions versus 415 Grade 2 lesions. So in the end I think we're looking at one common, unifying factor, that there is a differential response to these thicker lesions. The majority of the differential anatomic response is probably due to the difference in allocation of the two lesion types.

So I think really the issue is, is there really this differential response of Grade 1 versus Grade 2, yes, and acknowledging that difference in the labeling so that consumers as well as physicians are aware.

DR. DRAKE: Thank you.

DR. STERN: I think that's misleading. There was a 53/47 split each way in the distribution of hyperkeratotic lesions by anatomic site. It was 53 percent face for non-hyperkeratotic and 47 percent hyperkeratotic, and exactly the opposite on the slide I saw from the FDA. There's a 30 percent difference in efficacy. How a 6 percent difference between the two groups in the distribution of hyperkeratosis can explain a 30 percent difference in efficacy, maybe Dr. Kilpatrick can explain that to me, but when I saw those slides, I said I don't know of any corrective or adjustment mechanism that would bring those efficacies by adjusting and stratifying according to that. It may well be that hyperkeratotic lesions in the scalp do even worse, but that doesn't wash it away. I'm sorry.

DR. DRAKE: Rob, I'm sorry, I'm looking at that slide --

DR. STERN: That was in the presentation.

DR. DRAKE: I know, but I'm looking at that slide, and it says -- these pages aren't numbered, unfortunately, but it says that this is the difference

in lesion grade from different treatment sites? Is that the slide you're referring to?

DR. STERN: Yes, 53/47, wasn't it?

DR. DRAKE: It was a 57 -- face was 57 percent, scalp was 47 percent on the thinner lesions, but on the thicker lesions, the scalp was better than the face, at 53/43. If that's the slide you're referring to.

DR. STERN: I'm sorry. That's the difference, and so the difference is slightly greater, but still wouldn't make up a 30 percent difference in efficacy.

DR. DRAKE: But on this one, the scalp actually responded better than the face on the thicker lesions, if this is the same slide.

DR. STERN: I had thought that this is the distribution of lesions by anatomic site. Is that what this slide is? This is basically a 2x2 of type of lesions, location.

DR. DRAKE: I may have the wrong slide in front of me, then.

DR. OKUN: No, Dr. Drake, you have the right

slide. I guess my labeling of it was somewhat incomplete. The slide that you're referring to with those numbers, 57/43 and 47/53, that has nothing to do with response rate. That refers to the distribution of lesion grades --

DR. DRAKE: It's referring to lesion grades.

DR. OKUN: Yes.

DR. DRAKE: This is not response. Now, which slide talks about the response that Rob's referring to?

DR. OKUN: In terms of thickness, that would be the next slide in terms of looking at the response rate at Week 8, looking at the different subsets of thickness.

DR. DRAKE: Well, I guess I'm still a little confused, because I don't -- could you put the slide back up?

DR. OKUN: Actually, that would be great.

DR. DRAKE: Because I think this is an important issue, and let's discuss it with the slide, please. Because the lesion response rate is 88/78 just looking at lesion grades versus thick and thinner, but --

DR. STERN: If you look at 75 versus 48, I had said a 30 percent difference. It's a 27 percent difference in --

DR. DRAKE: But, Rob, I still don't know which slide you're talking about. So for me -- indulge your chairman. Let me see what you're talking about here.

DR. STERN: A hundred percent complete response rate, pooled pivotal trials, follow-up at Week 12, which to me is the ultimate ultimate, allowing for retreatments, and the difference in response rate, which I had remembered as 30 percent in the treated group in face --

DR. DRAKE: Rob, let's wait. Please, let's just get the slide up and then discuss it from there. It will take a minute, but I think it's going to be easier if we're all reading off the same page. That's what I'm just trying to get to. That way we can make an intelligent comment. Mainly me.

Tracy, just for future reference, these handouts are absolutely wonderful to trace and we love it, but it might help to put numbers on them so that

when we do something like this, we could even -- you know, it would be nice to have them numbered down in the right-hand corner. Just a suggestion.

DR. STERN: It's right after that diagram that goes down and down and down.

DR. DRAKE: In the meantime, while they're trying to find that slide, I want to ask a question of the committee. We're going to get all bogged down on this, and I don't want to, but with respect to hyperkeratotic lesions, I sense there's unanimity among the committee with having some labeling that clearly distinguishes between hyperkeratotic and non-hyperkeratotic lesions. Is that correct? May I have a show of hands?

(Show of hands.)

DR. DRAKE: Dr. McGuire suggests maybe even photographs would help. Nonetheless, I think for the agency's purposes, then, there is unanimity from the committee that there should be some labeling that distinguishes between hyperkeratotic and non-hyperkeratotic lesions in this study. That's one issue.

Jon?

DR. WILKIN: Is it the sense of the committee that if we just put response rates by grade, is that what you would like, or do you actually want limitation, or is this more of an informational thing?

DR. DRAKE: My sense, from what I've heard around the table -- and I guess I'd ask the committee to correct me if I'm wrong, but I think the committee wants the information out there so that people clearly understand what they're dealing with.

Is that a correct assumption?

DR. DiGIOVANNA: I think there are two issues. One issue is that the very hyperkeratotic lesions that were not studied, that it should be indicated that they were not studied.

DR. DRAKE: They were not studied, fine.

Is there any disagreement with that?

(No response.)

DR. DRAKE: Okay. Done.

DR. DiGIOVANNA: And the second issue is the thinner and the thicker lesions, and that's an informational issue.

DR. DRAKE: I think there's unanimity on

that. All right. Okay. So we've got that.

Now, I'm interested in the scalp stuff.

Phil?

DR. LAVIN: Thickness should also be broken out by face or scalp, because I think the efficacy data are there, it's just a question of showing it.

DR. DRAKE: Now, is this the slide you're referring to, Rob?

DR. STERN: Yes. So how I read this, if you look at the next-to-last column, to me, because of the retreatment, the last, best information we had on these individuals was at Week 12, some of whom had been treated once, some of whom had been treated twice, and the way I read this, if you look at the last column, for patients with face lesions, we had 75 percent complete response rate; for patients with scalp lesions, we had 48 percent. I had remembered 30 percent in my head as the difference, with the vehicles responding about the same, 10 versus 12. I had remembered 30 percent as the difference. I'm sorry, it's a 27 percent difference in efficacy.

DR. DRAKE: Shame on you.

(Laughter.)

DR. STERN: And the other point is, if you look at facial lesions from Week 8 to 12 in the treated group, it went from 68 to 75 percent. This is because some -- there are two things that went on here, as I understood it. One is that people who had unresponsive lesions or lesions that were still there at Week 8 were retreated, so the increase in 7 percent is partially due to a second treatment minus any of those that reoccurred, whereas if you look at Week 8 and 12 for scalp lesions, instead of going up with the non-responsive lesions being treated, there were more lesions that came back, according to the clinicians, than went away with the second treatment.

Obviously, the data might be there that you could say, well, how many really were additional ones going away versus going back, but the point is, within 4 weeks in the other we're already seeing more return of lesions than we are seeing additional efficacy from retreatment of lesions that were not initially responsive. And in something where you measure success -- most of us as clinicians measure success in 6 months

or a year, because that's how often we see these kinds of patients typically. To have recurrences outnumber additional successes in 4 weeks is not something that makes me happy, and 57/43 versus 47/53 -- I'm sorry, again, about that, I'm a little dyslexic -- to me doesn't explain a 27 percent difference in efficacy at Week 12.

DR. DRAKE: Okay. Phil?

DR. LAVIN: Don't be hung up about the 27 percent difference, because you aren't comparing face to scalp. You're really comparing vehicle to the treatment combination.

DR. STERN: It's only 25 percent when you put in that difference.

DR. LAVIN: Right. So it's the 68 versus the 75 and the 55 versus the 48.

I think the thing that you might want to be thinking about is what would this overall projection rate lead to at 1 year or at 6 months. In fact, I did that calculation just now. It turns out that you're projecting losing about 50 percent of the complete responders in 24 weeks. So I don't know what frame of

reference that gives you, but that's what the data from Dr. Okun's chart, his algorithm chart, would lead you to project.

So a sense of how you're doing here, I think that's the only thing that I would try to take from this. I wouldn't try to read in a comparison of face versus scalps.

DR. STERN: I was merely trying to say that adjusting for the difference of thicker lesions between face and scalp can explain these differences in efficacy.

DR. DRAKE: Okay. I'm going to, in the interest of time, take the chairman's prerogative. I don't want to argue this out right now. I think that the agency has heard that there is significant concern about this area, and it needs to be addressed properly in the labeling, and they can recirculate it. But let's not argue it out at the table.

Is that satisfactory with the committee? I think they've heard the concerns loud and clear.

Ms. Cohen?

MS. COHEN: I don't want to argue the point.

I just want it to be in plain language for consumers. That's all.

DR. DRAKE: I agree with you totally.

Dr. Wilkin and other FDA folks, are you satisfied with that? Okay.

Let's move to Question 2, then. The question here is, do we want to have 100 percent -- the question is, "To what degree does including information about efficacy as measured by the 75 percent or better complete response rate add to the information about efficacy as measured by the 100 percent complete response rate measure?"

I'll call for comments on this question. Phil?

DR. LAVIN: This is more from a perspective of robustness, and I think it is wise to have both pieces of information provided in the labeling. It gives someone a good confidence level of what the numbers are like if you don't have complete responses, and I think it is a clinically meaningful outcome to have 75 percent of all the lesions cleared.

DR. DRAKE: Does anybody disagree with that

statement?

DR. DiGIOVANNA: I don't disagree with it. I just don't know how much more information it would add, since it was so difficult to communicate the meaning of complete response, since it was used in two different ways, complete response of each lesion and complete response of an area.

DR. DRAKE: Any other comments? Fred?

DR. MILLER: I do think it's really important to get all the data in --

DR. DRAKE: Yes, I do, too.

DR. MILLER: And it's important to say that a significant percentage of these people had only three out of four lesions clear completely, and the language just has to be worked out so that indeed it is clear.

DR. DRAKE: Okay. Any disagreement with that last statement?

Dr. Wilkin, other questions from the agency on that?

(No response.)

DR. DRAKE: All right. Question 3. The question here is, does the language present in the label

and patient package insert satisfactorily forewarn patients about exposure to solar or incandescent light during the period between application of ALA and administration of the light?

Dr. Bob Jordon, and then Dr. Henry Lim.

DR. JORDON: The only package insert I have was in the original material, and it's 20-some, 25 pages long, with lots of technical stuff in it, and this is not what we're talking about here in terms of alerting patients as to what this therapy is and what kind of risks they take.

DR. DRAKE: Dr. Lim?

DR. LIM: The same point. I think we need to see what the language is going to be, but it should be there.

DR. DRAKE: And Dr. Miller?

DR. MILLER: In the information that we had, there was nothing about post-therapy protection, and they talked about 4 weeks having a decay period, but there was nothing about the post-treatment period.

And I had a question about fluorescent lighting. You know, patients are going to say, "Do I

have to become reclusive in my home? How covered do I have to be?"

DR. DRAKE: "I don't have to go to work tomorrow."

(Laughter.)

DR. MILLER: In lots of areas of Pennsylvania there are kitchens with banks of fluorescent lights. They're very bright.

DR. DRAKE: Okay. Dr. Mindel?

DR. MINDEL: I was not clear -- and I don't know whether a patient would be -- as to why, if the treatment is interrupted for any reason, it should not be restarted. And what does a patient do, then?

DR. DRAKE: That's a good question. Yes, it sort of leaves you hanging, doesn't it?

(Laughter.)

DR. DRAKE: That's a good pickup. I hadn't even -- I didn't even pick up on that.

DR. STERN: The good thing about ALA photosensitivity is, you know when it's happening, because it burns and stings. So the one thing that protects -- I personally believe what I think I'm

hearing from Ms. Cohen, that you need something very explicit designed for patients to be given at the time of treatment or before they sign on the line. But the nice thing about ALA photosensitivity is, it hurts when you're doing it. It's not like a delayed reaction, when you can be out in the sun all day and then 4 hours later realize you've overdone it. So most people know when you're face is stinging and burning, it's -- not that they're not going to get edema from it, but that's usually a hint that it might be a good idea to stop doing what they're doing.

DR. DRAKE: Other comments on this question?

MS. COHEN: It says here that the stinging and burning subsided between 1 minute and 24 hours. I mean, that's a big parameter, between 1 minute and 24 hours. So I don't know how they're going to explain that.

And also it says here that sunscreen will not protect people, and that's a very important point that should be on a consumer package, "Sunscreen is not going to protect you."

DR. DRAKE: Unless it's an absolutely opaque

sunscreen. Then it would.

MS. COHEN: A veil.

DR. DRAKE: Dr. Mindel?

DR. MINDEL: Just a suggestion, too. It says in there that it shouldn't be applied around the periorbital -- the drug should not be, but I would think it would be better to say that the goggles should be on when the drug is applied in the area around the eyes, or something like that, because that's really what you want, right?

DR. DRAKE: Well, it depends on the type of goggles. Some of them have great big, wide bands, and if you're trying to treat an area on the temple, it's hard. But you've got a very valid point.

DR. MINDEL: But no matter what, if it's hidden by the goggles, it's not going to be treated, and that's presumably --

DR. DRAKE: I agree with you, it's very important that they have the goggles there and on. And that's from our ophthalmologist guy, so we really have to pay attention.

(Laughter.)

DR. MINDEL: And I'm not going to say what I thought about these blinded versus non-blinded, either.

(Laughter.)

DR. DRAKE: Other comments on 3?

(No response.)

DR. DRAKE: All right. We're going to move to 4. We know what the sponsor and the agency have agreed to do. Now what we're being asked is what additional future studies would the committee recommend be performed, and I would like to open the discussion for that.

Dr. DiGiovanna, and Ms. Cohen after John.

MS. COHEN: Maybe he'll say it anyway.

DR. DiGIOVANNA: I think that given the frequency of actinic keratosis in skin cancer and the nature of this approach, I think that it is essential that a study be done to look at the treated lesions, in particular those lesions that have recurred in the area of treatment, to look for an increase in the incidence of development of skin cancer, particularly squamous cell carcinoma, which often does not behave in a well-behaved fashion like basal cell carcinoma usually does,

and can result in an increase in mortality. So I think that that is essential.

DR. DRAKE: Okay. Ms. Cohen?

MS. COHEN: I'm curious to know, when you apply the medication, in what form is it? Is it a cream? Is it --

DR. GOLUB: It's solution.

MS. COHEN: It's solution. Does it tend to run? Could it run?

DR. GOLUB: The way the applicator works --

THE REPORTER: We've got to get people microphones.

MS. COHEN: I beg your pardon. I know better. I'm sorry.

DR. GOLUB: The instructions with the applicator are to apply it to thoroughly wet the lesion that you're treating, without applying enough to run or drip. The Kerastick tip allows you very fine control over the amount of solution that comes out of there. So actually it will release some, and it can be absorbed back in. I mean, you can work with that Kerastick applicator. And I think after a brief experience with

it, the clinician will be able to control that.

MS. COHEN: Well, my concern is, as with Dr. Mindel, if people tend to perspire and you're doing this in a climate that's fairly warm, would it run in any way or get into the eye? Because I've read this carefully, and that worries me. It might not be a worry to you, but it worries me a little bit. Is that valid?

DR. DRAKE: The sponsor wants to respond to that.

DR. MARCUS: Yes, we can respond to that.

The issue about the eye was primarily, Ms. Cohen, because of the presence of alcohol in the solution that can burn. But our Phase III trials were done in warm, sunny climates where perspiration is very common, and there have been no instances of ocular adverse events seen as a result of running into the eye.

MS. COHEN: But you would put on your labeling, just in case by some strange reason it gets into the eye, how to clear it out.

DR. DRAKE: It's already in there.

DR. MARCUS: Yes, it's in there.

DR. DRAKE: Dr. McGuire?

DR. McGUIRE: I think the items in Question 4 are important. We have seen data that I think has been minimized. I don't think we've spent enough time on it, and I know no one wants to spend anymore time at this time of day, but I would like to see a follow-up on the cohort who were retreated at Week 8 and then relapsed. I'd like to see, in fact, the entire treatment arm. There were 56 who were retreated, and of that 56, 36 did not clear. That was with the second treatment. It seems to me that it's incumbent both on the sponsor and the agency to see what the histology of those lesions shows, as well as to find out what the histology is of the 14 who recurred after clearing at 8 weeks -- in other words, the 14 of the 117 who were clear at Week 8 and then relapsed by Week 12.

I emphasize that we're looking at a very narrow time frame here in a disease that lasts months and years, and it should be emphasized in whatever packaging you have that the data that we have is based on a 3-month study.

DR. DRAKE: I have to tell you, as a chairman's comment, I want to reinforce -- I agree. I

had on my list of comments to say what Dr. McGuire just said. I think there needs to be some histology on these unresponsive or quickly recurrent lesions. So I want to really reinforce that.

Dr. Kilpatrick -- I'm sorry, Rob, you were next. I apologize. Then Dr. Kilpatrick.

DR. STERN: Although it's probably clear from what I've said before that I think some longer-term studies are needed in terms of recurrence rates, type of lesions to recur and natural history, I think the reality is, we're going to have to use the surrogate measure of clinical actinic keratoses and not basal or squamous cell carcinoma in these areas, just because of power considerations, because of the incidence of these lesions. I mean, we can't expect the sponsor to set up a study that would have to enroll in a reasonable period of time many hundreds to thousands of patients. On the one hand, I think that would be not a reasonable burden for the sponsor.

On the other hand, I would emphasize that actinic keratoses are hard to monitor over time, both because of differences in clinical perception of them

and because they in fact change over time, and that simple follow-up of 70 or 100 or 150 patients in an unblinded way is in fact, to my mind, not likely to give one robust and interpretable data, that one really has to think very carefully not only about patient safety in the design of the trial, but a design of a trial that will minimize biases, both with respect to other therapies and especially with respect to observer biases.

So this is not an easy, let's-see-how-they're-all-doing-a-year-later kind of trial, in my mind, but on the other hand, I don't think we'll be able to determine the cancer risk.

DR. DRAKE: Dr. Kilpatrick?

DR. KILPATRICK: He's just stolen my thunder, because I was trying to say, but not as effectively --

DR. DRAKE: I should have let you go first.

DR. KILPATRICK: But I'd like to add onto Dr. Stern that I'd like to -- and pick up on what Ms. Cohen was saying. We're talking about a safety study of at least 70 additional patients. I don't think that's big enough. I'd like to see a follow-up study or some type

of postmarketing study of people who use this thing to see how effective the label is, what untoward effects they get if they do not follow rigorously what they're told to do in terms of exposure to sunlight, et cetera, et cetera.

Again, I'm on the same petard that Dr. Stern is. I don't know how much we can ask the sponsor to do of this, but I would like to see follow-up of the people using this after it's been marketed.

DR. DRAKE: Dr. Lim, and Dr. Miller.

DR. LIM: It's a question of clarification also. "Thirty of whom have Fitzpatrick skin type IV to VI," what is the purpose of doing it? Because especially in skin type V and VI, it's going to be very, very low to have actinic keratosis in those patients. It would be very difficult to find those patients.

DR. OKUN: Your point is very well taken. I would anticipate that the majority of those 30 would probably have Fitzpatrick skin type IV. And to answer the question about why we're interested in that, our concern, I think, stems from whether there would be differences in terms of postinflammatory hypo- or

hyperpigmentation as a function of increasing baseline skin pigmentation among the higher Fitzpatrick skin types.

DR. DRAKE: Dr. Miller?

DR. MILLER: I want to follow up on Dr. Stern's comments. I think that there's a lot of subjectivity looking at lesions that are healed or clear, and I think it would be good to have biopsies on lesions that are clinically clear on a group of those patients, so that are they truly totally gone after the therapy, and maybe this would explain some of this recurrence, you know, were they not gone to begin with.

DR. DRAKE: Actually, that's a very good point.

I think what you're hearing, Dr. Wilkin, from this whole group is that there's -- actinic keratoses are so fickle, because a certain percentage of them spontaneously remit, a certain percentage of them evolve into squamous cells.

And just as an aside, the most recent argument or discussion at the American Academy of Dermatologists was whether these are premalignant. That

terminology is being challenged vigorously. Most people believe these are in squamous cell in situs, they're squamous cell in situs, they're not premalignant, they're actual in situ malignancies. And I can tell you, I think there's a drift toward that, because that's the leading opinion of dermatopathologists and a lot of our skin cancer specialists, skin oncologists.

So I think what you're hearing is a level of discomfort with just saying they're gone, without some histologic proof or some follow-up of the biologic activity of these lesions to see what they do after they've been treated.

Is that a fair way to state that? Okay.

Elizabeth? Dr. Abel?

DR. ABEL: I would also like to see follow-up studies on patients who are on photosensitizing drugs, and perhaps to clarify that statement on clearing, is there clearing to a macular state with no obvious scale? To sort of refine that definition of clinical clearing.

DR. DRAKE: Dr. Lim?

DR. LIM: I just have a question to follow up on Dr. Abel's question. In terms of the

photosensitizing medication, I think that would add another layer of complexity. It would be very hard to analyze the data, number one, and, number two, in patients with PUVA, we know we put patients on PUVA as long as they're not on highly phototoxic medications, and we have had no problem with those.

I'm not sure, one, what additional information you would get, and, number two, I think it would make the data analysis so much more difficult to know what is going to be effective.

DR. ABEL: I think that there has to be some limited study on these patients for people to feel comfortable about treating them. If there is no data at all --

DR. LIM: Right. But on the other hand, we know the light source is at 417, and most of the photosensitizer is going to be at the UVA range. This is beyond UVA. So I don't think it's going to be affected.

DR. ABEL: Then it's not an issue, you're saying.

DR. LIM: I don't think it will be a

significant issue.

DR. STERN: I would agree with Henry that for most marketed drugs, this treatment is not an issue in terms of photosensitizers. I'd have to look at sparfloxacin and see how far it goes up, but the number of drugs I'd be concerned about is tiny.

DR. DRAKE: Dr. Wilkin?

DR. WILKIN: I think that's close to what our opinion was. We believe that if there was no photochemistry, there wouldn't be photobiology, and that --

DR. DRAKE: That's right. Details.

(Laughter.)

DR. WILKIN: And that in essence what we could do is, we could actually speak to the drugs that might be of concern.

DR. DRAKE: I think that's fine.

Now, Dr. Wilkin and the other folks from the FDA, have we answered these questions satisfactorily? Have you gotten enough information?

Don't people start packing up and leaving just yet. I'm not done.

DR. WILKIN: We have a lot of great information.

(Laughter.)

DR. DRAKE: Are there any questions that we've left unanswered? Tracy just wants to make sure you have an adequate answer for restrictions.

I think what I did, Tracy, is put that back into the -- I think they've heard all the comments around the table, and I think we'll let the folks at the FDA digest all this and come up with something reasonable. They've heard a variety of opinions.

Dr. Wilkin?

DR. WILKIN: Yes, I think what we heard from the committee was not really something along the line of restriction, but full disclosure in labeling --

DR. DRAKE: Full disclosure is what we heard.

DR. WILKIN: That we really describe the differences in scalp and with the hyperkeratotic lesions, and the two aspects that Dr. DiGiovanna mentioned, one, the hyperkeratotic lesions that were not studied, and then the different grades and the response at different grades. And also the follow-up, that

second treatment visit, we may want to craft a little more of that information for scalp into labeling as well. I think that's what our encouragement was to do.

DR. DRAKE: Anything else that the FDA needs from anybody? Are you okay with all this?

DR. WILKIN: Well, I would thank the committee and the invited experts from yesterday afternoon and the sponsors from yesterday morning and this afternoon. I think we had an amazing amount of really good information presented, and we had great feedback from the committee in answering questions on difficult topics, and three very different and difficult topics. Helpful for us.

DR. DRAKE: Okay. And I want to say two or three things.

First of all, I want to thank the sponsor for your time and effort and your research and the funds that you spend and the personnel you expend and the decisions you've made to help support research into products that will help our patients with skin disease. We're very appreciative. We understand it takes a lot of work, a lot of effort, and your life is sort of in

our hands here for a few moments, and that must be very stressful. But when you give us clear data and clear presentations, it's easier for us to help advise the FDA.

We just want you to know that we're grateful to you for your support of research into new therapeutics for skin disease. Our patients are all grateful.

And I want to thank the consultants for coming today. It's very nice.

I also want to thank the FDA. First of all, I want to thank Jonathan for your leadership. You know, there have been some new strides made. That session we had on hand dermatitis was wonderful. I mean, it just seems to me there are so many things that you're doing to make us able to do our job better. We're very grateful, from the community of dermatology. So I'd like to thank you and all your staff for your excellent presentations and organization.

And Tracy, our executive secretary, this has been a -- she didn't even eat lunch.

You get to eat supper tonight.

She hasn't eaten in 2 days. So we want to thank her for all her hard work. She has just gone full bore.

And thanks to the audiovisual people.

And most of all, I want to thank the committee. You guys are great. This is such a solid committee. I mean, you just really come forward with good, solid comments. There are no petty biases. I'm very, very proud of you, and I'm very proud to work with you. Thank you.

And, Henry, you have a question?

DR. LIM: One comment. During the last meeting, we didn't realize it was Joe's last meeting as a chair. I would like to, for those of us who had been in the committee for a year --

DR. DRAKE: Absolutely.

DR. LIM: To just express our appreciation for Joe's leadership.

(Applause.)

DR. DRAKE: And don't assume it's past tense. He still was doing a lot of help in here today. Over the last 2 days, I had a lot of sweet nothings in my

ear.

(Laughter.)

DR. DRAKE: Anyway, thank you, and you're going to all make your planes. Thanks for the hard work. Bye.

(Whereupon, at 3:56 p.m., the meeting was adjourned.)