FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

8:07 a.m.

Wednesday, September 10, 2003

Holiday Inn
Montgomery Village Avenue
Gaithersburg, Maryland

ATTENDEES

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ATTENDEES (Continued)

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C O N T E N T S

NDA 21-576, Methyl Aminolevulinate Hydrochloride,
(Methyl aminolevulinate cream, 168mg/g)
by PhotoCure ASA

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C O N T E N T S (Continued)

P R O C E E D I N G S

(8:07 a.m.)

DR. STERN: Good morning, everyone. This is the Dermatologic and Ophthalmic Drugs Advisory Committee to consider materials related to NDA 21-576, methyl aminolevulinate hydrochloride phototherapy. I'd like to ask permission to call this MAL-PDT so I don't have the same problems I had yesterday with pronunciation.

(Laughter.)

DR. STERN: So if it's okay with the sponsors, we'll refer to this as MAL-PDT, MAL standing for the word I just said, and PDT standing for photodynamic therapy, since we're considering both a chemical and a physical modality of therapy together. So if there are no objections, anyone can call it by the long name, but that is what I'll do.

So let's begin this morning by going around the table and everyone introducing themselves. I'm Rob Stern. I'm the chairman of the committee today and am from Boston at the Beth Israel Deaconess Medical Center and Harvard Medical School, and I'm a dermatologist by training.

DR. PLOTT: My name is Todd Plott. I'm Vice President, Clinical Research and Regulatory Affairs at Medicis. I'm the industry representative.

DR. RINGEL: I'm Eileen Ringel. I'm a dermatologist. I'm in private practice in Waterville,

Maine.

DR. TAN: I'm Ming Tan, Professor of Biostatistics at the University of Maryland School of Medicine, Department of Preventive Medicine and Epidemiology.

MS. KNUDSON: I'm Paula Knudson, the consumer representative, and I am an IRB chairperson and administrator at the University of Texas Health Science Center, Houston.

DR. DRAKE: I'm Lynn Drake. I'm a dermatologist on the faculty at Harvard and I'm based at the Massachusetts General Hospital.

DR. BIGBY: I'm Michael Bigby, yet another dermatologist from Boston.

DR. KING: I'm Lloyd King. I'm a dermatologist from Vanderbilt University in Nashville, Tennessee.

MS. KNUDSON: I'm Robert Katz. I'm a dermatologist in Rockville, Maryland, consultant in dermatology at Walter Reed Army Medical Center.

DR. SAWADA: I'm Kathleen Sawada, private practice, Lakewood, Colorado, dermatologist.

MS. TOPPER: Kimberly Topper. I'm the executive secretary for the committee.

DR. RAIMER: I'm Sharon Raimer, dermatologist, University of Texas in Galveston, Texas.

DR. TEN HAVE: Tom Ten Have, biostatistics and epidemiology, University of Pennsylvania.

DR. SCHMIDT: I'm Jimmy Schmidt from Houston, Texas in private practice.

DR. VAUGHAN: I'm Brenda Vaughan, dermatologist, FDA, medical officer.

DR. LUKE: Markham Luke. I'm a dermatologist. I'm the clinical team leader at FDA.

DR. WILKIN: Jonathan Wilkin, Director of the Division of Dermatologic and Dental Drug Products, FDA.

DR. BULL: Good morning. Jonca Bull, Office Director, Office of Drug Evaluation V.

DR. STERN: We'll now move on to the conflict of interest statement.

MS. TOPPER: 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 the meeting.

Based on the submitted agenda for the meeting and all financial interests reported by committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting.

We would also like to note that Dr. R. Todd

Plott has been invited to participate as a non-voting industry representative, acting on behalf of regulated industry. He is Vice President of Clinical Research at Medicis Pharmaceutical Company.

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 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 in any firm whose products they may wish to comment upon.

Thank you very much.

DR. STERN: I'd like to take a few moments to do two things. I thought, in thinking about this product where the indication is for the treatment of basal cell carcinoma, it might be good, particularly for the non-dermatologists, to have a little context at least as to how I see basal cell carcinoma and talk a little bit about currently available treatments for this tumor.

So basal cell carcinoma has a very high incidence in the United States. There are probably between three-quarters of a million and 1 million new and recurrent

tumors a year. A slight majority occur on the face and neck and a substantial majority in sun-exposed areas, if one includes the forearms and the distal legs.

The diagnosis, at least in my hands, is not always easy without histology. There are a number of lesions that I sometimes mistake for them. So many of us think it's always good to not be surprised and not do destructive things without knowing what you're treating.

They generally do not metastasize, but both primary tumors and recurrences can be very problematic with respect to substantial morbidity, although very low mortality, particularly when they occur on the head and neck where there can be substantial disfigurement, and with recurrent tumors, not rarely, interference with vital functions such as eyes.

The response to therapy varies with type, size, and location.

So from someone who has been treating these tumors for just over 30 years now and does mainly non-surgical treatment almost exclusively and refers on surgical treatment, the attributes of a desirable treatment for basal cell carcinoma from a patient's perspective is that it's quick -- and "quick" means low number of visits as well as low time at the visit -- painless, quick healing, limited wound care restrictions. You can go out

and play golf that afternoon, or at least two days later. Good cosmetic result, and that the tumor is unlikely to recur and need additional treatment.

The characteristics of a therapy from a physician's point of view that, in addition to meeting the patient's needs, maximize its usefulness in clinical practice, are simple. The therapy can standardize to limit interoperator variability. You know that no matter who does it, you're going to get a good result, that appropriate lesions can be easily identified. We spend a lot of time teaching residents that for this lesion in this location, you want to do this, but if there is this going on, you want to do that. So you want to have it so you know for any therapy what are in fact indications and counterindications and what among the alternatives put it at the top of the list, hence the choice for the individual patient.

That there is a very high response rate and that recurrences not only be infrequent, but one thing is, at least in my clinical experience, recurrences at the edge, particularly of superficial basal cells have a lot less associated morbidity than deep recurrences, which often take awhile to manifest themselves clinically, so often can grow large and involve deeper structures before, in fact, they're detected clinically.

So current therapies -- and I'll talk a little bit more about these in a second -- are electrodesiccation, curettage, cryosurgery, excisional surgery, Mohs surgery. I've left out topical chemotherapy with 5-FU and a whole variety of other less frequently used therapies. The sponsors are from a radium institute. I've left out radiation therapy, but I would say of the primary and recurrent tumors treated in dermatologic practice, well over 90 percent are treated by these four modalities, probably more than 95 percent. So these are the main things in terms of common practice that we talk about.

So questions for the committee about the product is, is there sufficient data for us to know how well it works? Is the therapy sufficiently clear; that is, clear in terms of indications and how to use it to be used effectively? And some questions I have that I hope we'll address is why did the results vary so greatly center to center in the study. And a question that is not for approval but as a clinician I only ask myself, does it work well enough to be a meaningful addition. The C was supposed to come out of there.

(Laughter.)

DR. STERN: I know you're hoping it would be an "addiction" in clinical practice.

(Laughter.)

DR. STERN: But a meaningful addition given our available therapies.

I talked to someone within the agency and we had a discussion about so what really are recurrence rates and wouldn't it be nice to sort of review for the committee the literature on recurrence rates. Fortunately, I have working with me a fifth-year Harvard medical student who is substantially more intelligent and higher energy than I am. Jean Lee was willing to prepare this presentation and review the literature with very little notice and, from my perspective, did an excellent job. So I'm presenting the materials here. These are articles I've all read at one time but not recently. I just went over the key data tables, but knowing Jean Lee, I think you'll agree this is an accurate representation, or I hope you'll agree.

So current modalities. Surgical excision is usually reserved for small, well-defined tumors on low-risk areas performed with 4 to 5 millimeter margins typically, although there's a huge variation in the application of surgery depending on the skill of the operator, the availability of frozen sections, a whole variety of things. But one would say those are some of the clear indications.

Cryosurgery is usually reserved for small tumors on cosmetically less sensitive areas because of frequent depigmentation and macular scars at the sites of

treatment.

Curettage and electrodesiccation. Usually for low-risk trunk and particularly for lower extremity lesions where it's often very desirable because you don't have to graft when you can't do, in fact, the primary closure on lesions.

Mohs micrographic surgery is used for high-risk tumors, used on the faced, basically a way for tissue preservation and almost certainly a lower risk of recurrence, and used in recurrent tumors where the anatomy has been changed so the usual landmarks by which we judge surgical or destructive therapies are absent and we need something to actually guide ourselves microscopically in looking at the individual case as opposed to applying guidelines.

So what are the predictors of basal cell recurrence? Size of tumor. Larger tumors recur more frequently. Clinically indistinct margins are more likely to be associated with recurrence. Location, particularly on the embryonic fusion plates which provide little resistance to tumor growth, particularly in the central face. Histologic type. It's a lot easier to cure nodular and superficial basal cells than it is sclerosing and morpheaform or mixed types. Perineural invasion tumors, again mainly on the face, are more likely to recur.

Recurrent tumors are more likely to recur again. If it was nasty the first time, although it's no guarantee of future behavior, the best prediction of future behavior is past behavior for these tumors, as well as many things in life. Previously irradiated tumors with X irradiation seem to have a high recurrence rate. And probably most important, after you standardize for all of these modalities, is the skill of the operator.

So the problem is what do you mean by a recurrence rate. We tried to look at three different kinds of recurrence rates. One is a raw recurrence rate, which is the total number of recurrences divided by the total number of tumors treated. A strict recurrence rate is the total number of patients with recurrence divided by the number of treated patients observed for at least 5 years. So if a person had three tumors treated and one recurred, they would be counted as a recurrent case since the modality failed in one of these tumors.

And the second and the way that, as far as I can tell, is almost never given in the label and the most appropriate, is a life table cumulative recurrence rate which adjusts for the rates according to the number of persons in each year of follow-up. But if you can find good life table studies of recurrence rates, please let me know.

So in the bolder, non-italicized type are in fact direct data on all of the following slides taken directly from the Thissen review, a systematic review of treatment modalities, which was published in the Archives of Dermatology about four years ago. In each of the slides, the ones in italics are basically what Jean Lee did in abstracting from other literature we found that was not cited primarily in the systematic review published four years ago.

Here we have for basal cell cancer for Mohs surgery, and you can see basically that recurrence rates, at least in the literature, range from .5 percent to about 2 percent in terms of these. There's one outlier, the Lundgren study, but in fact these were very high-risk sites and some sites are more likely to recur. I think many people accept the 1 to 2 percent recurrence rate, which will clearly vary substantially particularly with the operator's skill and with the location and type of tumors that the individual operator is operating on.

Surgical excision. Again, the same caveats about data sources here. The rates that you can see, in terms of cumulative recurrence rates, range in the 2 to 10 percent area at 5 years. Let me bring some attention to, again, how much rates will vary. Even looking in the Spraul study of 2000, which is about six down, looking at

very difficult periocular tumors where people try to get as small of margins as possible, with negative margins by histology at the time of excision, there was 2.3 percent recurrence, and of those tumors that had positive margins, there was a 12 percent recurrence rate. I think in looking at these data, most people would say it's about 5 and could be as high as 10 percent with a recurrence rate at 5 years.

Cryosurgery. Again, what you're doing and where you're doing it, size of lesions is evident here. If you look at, again, the eyelid which is particularly difficult to treat with large lesions, larger than usually recommended, certainly on the face with cryosurgery, a 16 percent recurrence rate at 5 years, but in fact for the other studies basically a 2 to 6 percent recurrence rate.

Electrodesiccation and curettage. Here we have similar to slightly higher recurrence rates as reported for cryosurgery. However, often smaller tumors are treated with cryosurgery more frequently, superficial basal cells. So you may have easier-to-treat tumors in the first case. Again, here you can see a range of estimates, and I think the most interesting one is the Dubin and Kopf study where he showed that if you look at trainees, you get a high recurrence rate, and in fact they showed in their own practices by board certified dermatologists a rate about one-fifth as high. So if you don't know what you're doing

with this, you probably shouldn't be doing it. If you know what you're doing, you can expect a recurrence rate for most kinds of tumors in the 3 to 6 percent range at 5 years.

So, in summary, the range of recurrence rates appears to be relatively similar for most physical modalities, including surgical excision, cryosurgery, electrodesiccation and curettage, curettage and electrosurgery, and curettage alone, although the data elements for the last two are sufficiently small that I didn't put them up. They're basically single-operator kind of limited studies, and that is excluding Mohs.

For a follow-up period of 3 to 4 years, this rate falls between 3 to 5 percent. For 5 years and more, the rate approximately doubles to 5 to 12 percent. Recurrence rates for Mohs are probably lower, probably within the 1 to 2 percent range.

So, in conclusion, the key predictors of tumor recurrence are size, site of location, histology, and skill of the operator. All of the non-Mohs modalities have roughly equal and excellent cure rates for basal cell carcinoma. Of those that are treated with high-risk characteristics, there's an increased risk of basal cell recurrence regardless of treatment modality with increasing time. This underscores the importance of looking at data

and adjusting for time and long follow-up time for evaluating the effectiveness of therapy.

Thank you.

Dr. Wilkin?

DR. WILKIN: I can say a few words. From time to time, FDA as a scientific regulatory agency needs access to highly qualified expert advisors who can speak to the clinical science and also to the values, the values in clinical judgment, societal values, that relate to standards of care.

The topics which may come before an advisory committee such as this include new products, that is, products that are new in a line. PhotoCure has submitted an application for methyl aminolevulinate with photodynamic therapy for nodular and superficial basal cell carcinoma, and that would constitute a new product and a new line. So it's a reasonable topic for this committee to think about.

PhotoCure will begin the analysis of the data this morning. They will lay everything out, and then FDA will speak after that and comment on some aspects of our analysis that might be somewhat different, but it's another way of looking at the issues.

Then we were seeking expertise, dermatologic surgical expertise. We actually contacted over a dozen dermatologic surgeons and only one is able to join us and

not until this afternoon. So I did contact Dr. Stern last week and alerted him to that, and I think it was a very helpful overview that we just heard because I think that may enter into the discussions among committee members what is already out there for nodular basal cell carcinoma and how this product may fit into the overall armamentarium.

Along with that, I would encourage the members of the committee to think about the potential tools we have in labeling. When I say labeling, I'm talking as an FDAer. It's what most people call package inserts. There is a portion of the Code of Federal Regulations, 201.57, that sort of outlines how we think about labeling. It gives us, for example, the order in which things show up in labeling, its the description section, and then clinical pharmacology. The third section is the indication section. In the indication section, there is the potential for elaboration to define the population that is most appropriate for a particular drug product.

Also, some other sorts of information can be added into that section that would be helpful to a clinician. Dr. Drake is with us today, and we have known from previous advisory committees that she's very helpful in crafting wording which is supportive, informative, but doesn't box clinicians in. I think that's basically the key piece. So I think we would like to hear that also from

the committee, when you are answering the different questions, if you can think about labeling options that may be helpful to the practitioner.

And then something that's not on the agenda but will no doubt be observed today, because this is the last day of the meeting of this advisory committee this week, possibly around 11:30 or noon, you'll start seeing luggage pile up on the wall. I would just say to the new members of the advisory committee that this committee has a tradition, under Dr. Stern and his predecessor, Dr. Drake, as chair, that the committee has stayed until everything has been thoroughly discussed. So I'm happy to say that we'll be able to thank everyone at the end of the day for making it through and giving us good advice.

DR. STERN: Thank you, Dr. Wilkin.

We'll next go on to the presentation by PhotoCure of the MAL-PDT application.

DR. HANSSON: Dr. Wilkin, Mr. Chairman, members of the committee, ladies and gentlemen. My name is Vidar Hansson. I'm the President and CEO of PhotoCure. I have a medical background from '69 at the University of Oslo. I have a Ph.D. primarily from research done in the United States in Chapel Hill actually in molecular endocrinology and molecular cell biology. My experience in the medical field is six years as an associate professor in pathology

and actually 21 years as a professor in biochemistry and molecular cell biology. And for the last six years, I've been the CEO of PhotoCure.

I will just say a few words about the rationale for choosing MAL. I agree with you. We will use MAL-PDT rather than the full name to make things simpler for us.

We will have a regulatory overview by Dr. Clementi. Dr. Hestdal will make a brief overview of our clinical program. Dr. Pariser will review some of our important studies in what we call non-high-risk or low-risk basal cell carcinoma, and Dr. Murrell will then review two of our studies on what we call high-risk basal cell carcinoma. Of course, safety will be addressed by Dr. Posner, and Dr. Hestdal will finally try to sum up the benefit-risk ratio of this new treatment.

First, a few words about PhotoCure, which is a very new company. The first employee was the 2nd of January 1997. It springs out from the Research Institute at the Norwegian Radium Hospital, which is the largest comprehensive cancer center in northern Europe. It has a research institute of more than 200 full-time employees, and PhotoCure is one of several scientific experiences and one of the two commercial activities coming out from this institution.

This just lists some properties of methyl

aminolevulinate. MAL actually is an ester monocarbon substitution on the carboxy group of aminolevulinic acid and, for reasons we only partly know, causes quite dramatic changes in the biological properties of this molecule in the rapid and efficient induction of intracellular porphyrins primarily in cancer cells and almost not in normal cells, and for other reasons we also only partly know, a very low ability to cross the basal membrane and very low uptake into the body. Upon illumination with red light, this induces photoactivation of the intracellular proteins and death of the tumor cells but not the surrounding normal cells and by a process that recent publication means comes through apoptosis.

This is just an example of MAL penetration into a small nodular lesion. You can see the demarcation of the basal membrane here, some tumor, some normal lamina propria, and normal tissue around. You see a freeze crack here in the frozen section. You see a cystic clearance here which is actually a central necrosis in the tumor that you frequently see in nodular lesions.

The MAL cream was applied for 3 hours, and this is then a fluorescent image in a CCD camera where you activate by blue light and do the red fluorescence recording and you shoot the photographs.

This really shows the very low induction of

photoactive porphyrins of MAL cream compared to the parent compound, the aminolevulinic acid. If you apply a cream containing MAL or ALA for 3 hours to the inside of the underarm of a human being and you look at the fluorescence of photoactive porphyrins after activation by blue light, with the MAL cream you see little or no fluorescence, whereas with the parent compound you actually see a very strong fluorescence even in the normal skin.

For practical purposes, there's very high selectivity between the basal cell carcinoma. Here you see a large basal cell carcinoma, 12 centimeters in diameter, on the shoulder of a human being. Here you go into the dark room. You activate the porphyrins with blue light. You record the red fluorescence. This is actually what you see with your bare eyes. You can actually shoot the picture with an ordinary mirror reflects camera, and you see how the fluorescence is really located and demarcate the tumor and not in the surrounding normal tissue.

This cartoon actually tries to illustrate the mechanism by which MAL-PDT works. You put on the cream for 3 hours and 8 molecules of MAL makes a porphyrin, and then upon illumination with red light, makes reactive oxygen species and primarily singlet oxygen that kills the cells.

This shows how this extreme lesion cell activity and penetration throughout the lesion gives the

possibility for successful tumor removal and tissue conservation in a case as shown here. This dotted line actually shows the tumor, and they started, of course, with Mohs surgery. This was on anticoagulant therapy and because of excessive bleeding, as well as problem with the anesthesia, they had to stop the Mohs surgery and they had a small graft on the tip of the nose. When he came back after a while, he was put into our high-risk study in Australia, and at baseline and 3 months, he was in complete response. He still has a sustained complete response verified 24 months after treatment. I think this is just one example of how MAL-PDT can be used in certain situations where surgery may not be appropriate.

I will then give it over to Dr. Clementi, our regulatory consultant and U.S. agent. Please, Dr. Clementi.

DR. CLEMENTI: Thank you, Vidar.

Methyl aminolevulinate, or MAL-PDT, is not going to be the trade name for this product. We are searching for a trade name, so we'll work with MAL-PDT today.

It is a combination product, both a device and a cream, being reviewed. The CureLight broadband model CureLight 01 has received an approvable letter from CDRH and methyl aminolevulinate cream is the discussion that

we're entertaining today.

We followed a reasonably conservative regulatory path. We met with the division many times. We have two applications with this division, one on actinic keratosis and one on basal cell carcinoma. We're not talking about actinic keratosis today, but many of the comments we received on the chemistry and manufacturing controls and on the preclinical sciences were applied to our development program in basal cell carcinoma. As you can see, we met often. We filed our IND for AK in 2000. That was preceded by our IND in December of 1999, and our NDA was filed in February of 2003.

We did have a total of six major meetings with the division. We enjoyed all of them. We found all of them productive, but we generated a lot of questions in the process. So for AK we had our three traditional meetings, and for basal cell carcinoma, we had our pre-IND meeting, our end-of-phase II in March of 2000, and our pre-NDA meeting in June of 2002.

Thank you very much. I'd like to turn the presentation over to my colleague and friend, Dr. Hestdal.

DR. HESTDAL: Thank you. Chairman, ladies and gentlemen, I will go through a summary of the clinical development. That will be discussed in more depth in a later presentation.

My name is Kjetil Hestdal. I'm the Vice President of Research and Development at PhotoCure. I have a medical degree and have a Ph.D. in basic immunology obtained at the National Cancer Institute here in Bethesda.

The clinical development program assessed different aspects. Of course, we had to identify optimal cream concentration, cream application time, and the illumination parameters. This was established in phase I/II studies.

The efficacy of MAL-PDT in BCC was demonstrated in two adequate and well-controlled studies in primary nodular BCC using vehicle as the control. Furthermore, we also have a study of the relative efficacy in primary nodular and superficial BCC using surgery and cryotherapy as comparators. We have obtained supportive evidence from two studies on the efficacy and safety of MAL-PDT in nodular and superficial high-risk BCC.

The safety profile that will be shown to you later is based on patients from clinical trials both in BCC and AK, and in addition to that, special safety studies.

If we go to the dosing parameters, the assessment of cream concentration, cream application time, and light dose were assessed in three different studies. It's important to say that in two of those studies, we used the fluorescence ability of photoactive porphyrins to

establish the dose penetration and selectivity. In addition, we had a phase II study that established the safety. So the cream concentration comes from one study where we actually measured the photoactive porphyrin fluorescence in the depth of the lesion using three different concentrations of the cream.

The cream application time was done also measuring the fluorescence from the photoactive porphyrins both in BCC as well as in the normal tissue and established a selectivity during 28 hours of cream application.

Lesion penetration was also assessed in the same way as the cream concentration using two different time points.

Clinical efficacy was then established examining the efficacy of the four different time points of cream application.

The light dose. We also used the ability of the photoactive porphyrins and the activation and we looked the photobleaching of this when you do the illumination.

The conclusion of the dosing is that the highest penetration in the BCC lesion was obtained in the highest concentration examined, 168 milligrams per gram. The application time was assessed based on the optimal penetration, the highest time point for selectivity, and the clinical efficacy turned out to be 3 hours. The light

dose was established when we obtained complete photobleaching using red light of a wavelength of 570 to 670 nanometers and a total dose of 75 Joules per square centimeter.

This is just a brief example of the method. It consists of a lesion preparation using a curette, it has cream application, and then you have illumination for 10 minutes.

DR. BIGBY: Are the patients anesthetized for the curettage step?

DR. HESTDAL: If you allow me, if it's okay with the chairman and you, to take the question when we are finished the discussion, I think it will be addressed by our clinical experts. Is that okay?

DR. STERN: Sure.

DR. HESTDAL: So the cream concentration was 160 milligrams per gram and was applied in a 1 millimeter thick layer on the lesions and 5 millimeters on the surrounding skin. 3 hours under occlusive dressing of the cream. The light dose, as I said, was 75 Joules using the red light. Generally, two treatment sessions, 1 week apart, constituting one treatment cycle, were used and the possibility of a second treatment cycle 3 months later in case their lesion showed a non-complete response.

This is a picture of the light that has been

used in all clinical studies, and the light is obtained from a halogen light bulb. The lens system in the lamp head provides focus and homogeneous light. There are also filters that remove blue light, UV, and infrared light and in this way, with these filters provides a red light with a specific wavelength between 570 and 670 nanometers. The light intensity has been 50 to 200 milliwatts per square centimeter and it's dependent on the distance from the treatment site. Again, this lamp gives a circular treatment area of 30 to 55 millimeters in diameter.

This lamp, as I said, has been used in all clinical studies except for 6 patients where a light source with similar physics was used. However, that lamp had a bigger light field.

Throughout the whole program, we have tried to standardize the methods. In regard to efficacy, we examined efficacy both on the patient level, as well as on the lesion level. Patient means that a patient can have several lesions. For the patient to be considered a complete response, all lesions on that patient have to be in complete response. Then we have assessed the lesion response on the individual lesions, and this is done both clinically as well as in four studies with histological verification using in the high-risk population a punch biopsy, while in the two vehicle-controlled studies, we

have used serial sectioning.

The recurrence has been assessed annually by clinical assessment of the lesion site. Of course, we have assessed the cosmetic outcome both judged by the investigator as well as the patient, and safety has been obtained collecting local and non-local -- that means systemic -- adverse events, and from five phase I/II studies we obtained hematology and biochemistry parameters.

What has been important for us is to have a consistent study population in different studies. So the study population that has been targeted in our program has been low-risk superficial and nodular BCCs. This has been included in four controlled studies, while we also in two studies have examined the efficacy and safety of MAL-PDT on high-risk nodular and superficial BCCs.

The definition that has been used to include patients or characterize the lesion as high-risk has been lesions in the H-zone or on the mid-face and ear. The lesion could also be included if they are large fitting into specific characteristics depending on the lesion site, if the lesion also had a recurrence or was recurrent after previous treatment, because it was considered high-risk, and if lesions appeared on very severely sun-damaged skin.

It is important information that in all the clinical studies, both in the high-risk as well as in the

low-risk, morpheaform or infiltrative lesions have always been excluded. It is also important to mention that in the low-risk superficial and nodular BCC studies, these high-risk lesions were exclusion criteria.

So there have been two programs that have gone in parallel. That is the efficacy evaluation of MAL-PDT both in low or non-high-risk BCC in four controlled studies, two vehicle-controlled and two active-controlled studies, and then two studies in the high-risk population.

The safety of MAL-PDT has been obtained through phase I/II and III studies and will be presented both from the AK program that consisted of 383 patients and from the clinical studies in BCC containing 538 patients. In addition to that, the safety is also obtained from a compassionate use study with more than 1,000 patients in Norway, and we have also conducted three special safety studies in healthy subjects. Then we also have post-marketing data for more than 35,000 AK and BCC patients from Europe.

Thank you. Then I will give it over to Dr. Pariser.

DR. PARISER: Thank you, gentlemen. Thank you to the group. As long as my voice holds out, I would like to spend the next few minutes talking about the clinical trials that I was involved in as an investigator, in one of

them, the four trials that were just mentioned, and then make some comments about basal cell carcinoma in general and where this treatment might fit into the regimen and armamentarium, into the tool box that Dr. Stern described that's available for treatment of skin cancer now, basal cell now.

Well, in the United States, as well as elsewhere, eradication of the tumor for treating basal cell carcinoma is usually and almost always the goal of treatment and is the primary goal that is sought. Cosmesis is extremely important and maintenance of maximum normal tissue preservation as well. Only in certain selected cases is palliation or observation really a goal.

Dr. Stern reviewed very well the standard treatments that we have now for basal cell carcinoma, both high-risk and low-risk. He rightly talked about the 90 percent or more of patients that are treated by the primary methods of electrodesiccation and curettage, cryosurgery, excision, and Mohs. But I want to try to frame photodynamic therapy as in the "other" category, the category where we think about radiation therapy, topical 5-FU, and other treatments for in situations where any surgical modality may not be the appropriate treatment.

As we decide what to do and how to treat basal cell carcinomas clinically, we look at various factors:

the anatomic location, the histologic type, whether the tumor is primary or recurrent, how big it is, and the patient characteristics too, the cosmetic concerns of the patient. We may treat a 25-year-old with a basal cell a little differently than a 75-year-old. Patients may have preference for various treatments. There are comorbid conditions or concomitant illnesses that affect the choice of therapies frequently, as well as the physician's skill that was mentioned by Dr. Stern and preference. Of course, we have to think about cost of treatment.

There really is no uniformly established standard of care for basal cell carcinoma. We all do this every day. All clinicians and dermatologists treat basal cell carcinomas every day, but there really are essentially no randomized controls of the modalities of treatment we currently use all the time. The heterogeneous population of patients and of lesions makes it difficult to produce algorithmic guidelines which would apply to treatment of all basal cells. So the lack of uniformity in the populations and the lack of outcomes make reporting difficult, and there really are no studies that adequately compare, in the same study side by side, cure rate, cosmesis, satisfaction, and cost. The study that Dr. Stern cited is, of course, a meta-analysis and very good data, but doesn't compare all the modalities in the same study.

So the meat of what I want to present to you, the sort of core of this development program of this drug, has been the two double-blind, vehicle-controlled studies and two active comparator studies, the active comparators being excisional surgery in one study and cryotherapy in the other study. All of these four studies which I'll describe for you were prospective multi-center, randomized studies with parallel group design.

Of primary importance is the study of MAL-PDT in low-risk basal cell carcinoma, and these are the vehicle-controlled studies known as 307 and 308.

The 307 study was conducted at 8 sites in the United States. Here is the list. I was an investigator in this trial. The pathology for this was all done in a central lab in Rochester. Dr. Gibson was the pathologist who examined all the specimens.

The Australian study, identically designed, was carried out in seven sites in Australia, and Dr. Murrell is here as an Australian investigator, and these are the folks who did this particular study.

The inclusion/exclusion criteria for the studies were exactly the same. Included were only primary nodular basal cell carcinomas not previously treated. The exclusion criteria for these lesions were large lesions, and "large" was defined differently for different places on

the body: 20 millimeters for extremities, 30 millimeters for trunk, and 15 millimeters for face. Also excluded were lesions located in the mid-face, those ones which are a little more problematic clinically, and morpheaform lesions were excluded from all the trials.

In order to precisely and accurately identify where the lesions were and to be able to be sure that the proper lesion was being evaluated in the follow-up periods and to guide where the excision was going to be at the end, India ink tattoo marks were used to mark the lesions. I will show you a little picture about how that was. The four tattoo marks were excised at the end of the study during the surgical excision.

So here's a small tumor and I think you can see the four India ink tattoo marks at the visual external margins of the lesion which were used to locate the lesion during the study and were used as a guideline for excision at the end.

The specimens were all examined histologically in a breadloaf fashion in the central laboratory with sections cut not in Mohs fashion, but in breadloaf fashion, as you see indicated. Multiple sections were taken. In the 307 study, this is the number of sections examined per millimeter of length of the specimen, so just under one in the 307 and almost one-and-a-half sections per millimeter.

So there was quite a bit of sectioning done in the breadloafing of that piece of tissue.

The investigators were trained on the technique of performance of the MAL-PDT by on-site demonstrations and each individual investigator site both in the U.S. and in Australia. The same two trainers trained all the investigators. Some of us even had the chance to visit Oslo and learn how to do it in Norway. There was an instructional video that was supplied to all the investigators, as well as the written instructions which were in the protocol. So these are these items supplemented the written instructions.

Now, there was a question before about the lesion preparation. The idea of the lesion preparation was not to do a therapeutic curettage by any shape of the imagination. The idea was to remove the surface epidermis, a bit of the tumor to allow the medication to penetrate and the light to penetrate into the depths of the tumor. This is something which was done without anesthesia, to answer the question, and it was a very surface debridement not intended to be a therapeutic curettage. We will have a discussion about whether in fact in some patients it may have been a therapeutic curettage, but that certainly was not the intent.

The primary efficacy variable of the study was

the complete histologic response in a patient. So for a patient who may have had multiple lesions to be counted as a responder for the primary efficacy variable, all the lesions within any individual patient had to be totally and completely cleared histologically. That was the endpoint of the study.

Secondary endpoints that were looked at were the histologic rate by lesion as opposed to by patient, the clinical outcome by patient and by lesion, as well as the cosmetic assessment by the investigator and the patient.

Also, the safety variables were looked at as well and they'll be assessed in a separate presentation on the safety from all the studies combined.

Definitions which were used in the study and which I'll refer to in the results here are as follows. A patient histologic response assessment. A complete response was defined, as I said before, in a patient where all lesions within that patient had a complete histologic response, and the meant complete disappearance of all tumor cells. And a non-complete response was not complete disappearance of tumor cells.

In terms of the clinical efficacy evaluation, a complete response was defined as complete disappearance clinically of the lesion, no perceptible lesion clinically. A partial response was defined in a lesion where the

longest diameter of the lesion was decreased by half or more, 50 percent of more, and a patient was judged as having no response -- there may have been some change in the diameter of the lesion, but less than 50 percent. Those patients were deemed to have no response. And then the term "progression" was used if the lesion enlarged by 20 percent or more. So those were the definitions for the trial.

In terms of the cosmetic outcome assessment, the signs assessed were scarring, pigmentation changes, atrophy, induration, and erythema. Those were graded according to the definitions that you see on the right side of the slide.

Now, this is the flow diagram for the studies 307 and 308, the two placebo-controlled studies. Now, the patients, after randomization in the study, either had MAL-PDT or vehicle-PDT which was a sham PDT procedure with the same lesion preparation, the same application of medication, the same illumination, only the active ingredient obviously was not in the cream. These patients received one treatment cycle, which is defined as two treatment sessions 1 week apart. So the MAL-PDT or vehicle-PDT was applied and performed 2 weeks apart, and then the patients were followed for 3 months.

At the end of the 3 months, the patients were

judged as having a complete, partial, or no response, and if they had a complete clinical response, they went into a follow-up period where 3 months later, the lesion was excised in a breadloaf fashion that I described for you.

If they had a partial response, they were treated with another cycle of PDT, defined as two more sessions 1 week apart. That was either the vehicle or the active.

If they had no response, the lesion was excised and they left the study.

Then those patients who had a second treatment were followed for 3 months after that and were either clinical responders, in which case the lesion was excised, or an incomplete response, in which case the lesions were treated and the patients left the study.

There were 65 patients with 80 lesions included and treated in this trial, the 307 trial, that were randomized roughly 50-50 to the MAL-PDT or the vehicle-PDT. Two protocol deviations happened to have been in the active drug group for the reasons that you see at the bottom of the slide, leaving the following numbers in the sample size of the study patients.

In the 308 study, the numbers are similar and discontinuations were similar. You can see the reasons for discontinuation there. So the total numbers of patients

are per protocol, as you can see in the bottom boxes.

Looking at the demographics of the patients in both studies, there really was no significant difference. The only thing that does show up on this slide is that in the 308 study there's a little discordance in the gender of the patients. That really was not deemed to have any clinical relevance.

Most patients had 1 lesion that was treated, the large red bar. A few patients had 2, 3, or 4 lesions. Remember that for a complete response in a patient who did have multiple lesions, all of the lesions had to be histologically cleared. So a few more in the 307 and a few less in the 308 with multiple lesions, but the vast majority of patients did have only 1.

Now, this is the primary efficacy variable, the meat of the presentation, if you will. This is the patient response rate to the study in the 308 and the 307 by patient listed first and then by lesion. So the primary efficacy variable of the study which was the patient complete response: in the MAL-PDT, 67 percent in the 308 and 78 percent in the 307 study, as opposed to 18 and 33 in the vehicle-PDT. This is the primary efficacy variable which does have a greater than .001 p value. So that's the cure rate of this treatment in this study, displayed on an intent-to-treat basis.

Lesion response, actually very similar numbers as opposed to patient response.

There really was not any significant treatment-by-center interaction in the primary efficacy variable, although there was some variation in the center-by-center results. In every center there was a higher response rate for the MAL-PDT compared to the vehicle-PDT, and there were two sites with very small numbers of patients that did have extreme values that contributed 20 percent of the data in the primary analysis.

Looking at the cosmetic outcome of the patients in both the 307 and 308 studies, as you can see, the vast majority of patients and investigators rated the cosmetic improvement as good to excellent. No one rated it poor.

So the efficacy conclusions from these two blinded vehicle-controlled studies, the primary efficacy variable was demonstrated and that was a statistically significant difference in the active versus placebo group in these two controlled studies based on the primary endpoint of complete histologic clearing.

Now, I'd like to switch gears and talk about two additional studies, and these are active comparator studies which were done outside the U.S. and in which I personally was not an investigator.

There are 13 sites in the Europe in the 303

study. This is the 303 study, a randomized trial, obviously not blinded, but a randomized trial of MAL-PDT versus simple excision for primary nodular basal cell carcinoma conducted by these 13 centers.

The second study we'll talk about is MAL-PDT versus cryotherapy in superficial basal cell carcinoma, again a prospectively randomized study conducted in these 12 sites in Europe.

Now, the main objective of these two studies looking at them together is to compare the response rate in a controlled population in a prospective fashion of these two modalities, cryosurgery and excisional surgery, to MAL-PDT.

Now, in designing this protocol, the protocol was designed to pick up a clinically relevant difference of 15 percent or more in the response rate. So the study was designed to pick up a greater than 15 percent difference. In order for that to happen, the confidence limit had to be above the negative 15 percent.

Secondary objectives were the cosmetic outcome, adverse events in all the studies, and long-term follow-up.

The inclusion criteria for these two studies were similar to the others in the case of untreated nodular basal cell or superficial basal cell carcinoma and the patients and lesions had to be suitable for treatment with

the comparator to be randomized in the comparator study. The high-risk lesions were excluded. The morpheaform lesions were excluded and the infiltrated lesions were excluded, as defined previously.

So you'll see this looks pretty similar, the study diagram. The patients who were randomized to MAL-PDT had the same cycle of two treatment sessions, 7 days apart; 3 months later were judged to have a complete or non-complete response. The non-complete response patients had another cycle of PDT, two sessions 7 days apart, and then were followed for 3 months, as were the ones who were complete responders after the first treatment cycle.

Histology was not done at the end because this study involved long-term follow-up.

So those patients who were randomized to surgery in that same study had the surgery, and 3 months later were evaluated as either complete responders or non. If they were complete responders, they went into the follow-up, and non-complete responders were dropped from the study.

In the comparator study versus cryotherapy or cryosurgery, these patients, those who were randomized to the MAL-PDT group, had one treatment session of MAL-PDT and 3 months later it was decided whether it was a complete response or non-complete. The non-complete had the usual

two treatments in the treatment cycle, and responders went into follow-up. It's a bit complicated, but the ones who had cryo in this study were followed at 3 months after the cryo. The complete responders went into the follow-up, non-complete responders in the study were retreated with cryo and then were either deemed to be complete responders and went into follow-up or non-complete. So I hope I've explained that satisfactorily.

In terms of the excisional group, this simple excision was done with a 5 millimeter margin, a very generous margin for excision of basal cell carcinoma, probably much more generous than done in clinical practice when excision is done for basal cell carcinoma.

The cryotherapy, just the details of how that was performed. It was done with liquid nitrogen. The lesions were frozen to an icefield of a 3 millimeter margin around the lesion. It was allowed to thaw for two to three times the freeze time, and then a second cycle of cryotherapy was applied for a minimum of 20 seconds.

In the 303 study, 103 patients randomized; in the 304 study, 120. So those are the n's that we're dealing with.

Demographics in the two studies together showed no real difference in the populations going into these studies.

In the excisional surgery study, most patients had 1 and only a few patients had 2 lesions. In the comparator study, a superficial basal cell carcinoma with MAL-PDT, many more patients had more than 1 lesion, and that's of course a common presentation for superficial BCC.

This is looking at the primary efficacy variable 3 months after the treatment. The patients who had the MAL-PDT, 45 out of 50, or 90 percent, met the criteria of cure; that is, they were cleared. The comparator, surgery, was 98 percent. The confidence limits for this particular study, displayed here as MAL minus comparator, do not encroach into that 15 percent window that we talked about earlier. So these patients did meet the primary efficacy variable.

Similarly, the MAL-PDT versus cryo was even better, 95 percent. It actually beat the cryo and certainly was well within that 15 percent. In fact, it was on the other side. That was patient complete response rate.

Looking at lesion complete response rate, the MAL-PDT versus surgery, looking at lesion by lesion, 91 for MAL-PDT, 98 for surgery, and in the cryotherapy, 97 for MAL-PDT and 95 in this population.

Looking at the cosmetic outcome, pretty much all surgery by definition leaves scars, and so scarring

would not qualify as an excellent improvement most of the time. But you certainly can see that the investigators and patients rated the MAL treatment excellent or good, much higher than the surgery, particularly the patients who seemed to like it more.

Looking at the cosmetic outcome of the cryo versus MAL-PDT, the same things are found. The cosmetic improvement was rated much higher with MAL-PDT than it was with cryo. Dr. Stern so rightly talked about those hypopigmented scars that we get from cryo all the time.

Now, this is an attempt at a life table to follow over time what the recurrence rates may have been, and I'll show you what's available to date about this. At the 2-year follow-up point, 8 out of 53, or 15 percent, of the MAL-PDT patients were treatment failures, and 1 out of 52, or 2 percent, of the surgery patients were treatment failures. This line and this line are the number of patients who are missing, lost to follow-up, and not included in the table.

So here is the table going out to 24 months. Now, this is going to be extended all the way to the 5-year point, which is how the study was originally designed. But you can look at the time to treatment failure in the top line for surgery at the data points indicated and the MAL-PDT at the data points indicated.

Looking at the cryotherapy comparator study showing the same data, there was a 25 percent treatment failure at 3 years. This is new data, and I think this is part of the information that the agency has. This is a little longer on the cryo 3-year follow-up. 25 percent treatment failure estimate for the MAL-PDT, about the same estimate for the cryo. Those curves are pretty much superimposable.

So the conclusions from these two comparator studies were that MAL-PDT did give a similar initial response rate and a sustained response rate very similar to cryotherapy in this prospective randomized trial versus cryotherapy for superficial basal cell carcinoma. Regarding the MAL-PDT response in excisional surgery for nodular basal cell carcinoma, there was a similar initial response but a lower sustained response rate compared with surgery, still however meeting the criteria of 15 percent. Also, the other conclusion was that the MAL-PDT was judged by investigators and patients to have a superior cosmetic outcome.

I will now introduce Dr. Dedee Murrell to talk about some of the studies in the higher-risk patients.

DR. MURRELL: Thanks, David.

I'll be presenting the results of MAL-PDT in the high-risk basal cell carcinoma patients. In addition

to being an investigator on one of these studies, because I'll be presenting two, I was also an investigator on the 308 study that you just heard about and also a randomized controlled study of MAL-PDT for actinic keratoses.

I'm a dermatologist trained in the United States at Chapel Hill, have trial experience at Duke, and was on the full-time academic faculty at NYU and Rockefeller prior to going into clinical academic dermatology in Sydney. Of course, practicing in Australia, I treat a lot of patients with skin cancers and refer patients to Mohs surgeons there too. So the practice is not that dissimilar from practicing here.

In Europe, these were open, uncontrolled studies in a high-risk group of patients, and the dermatologists and the sites shown in Europe are eight, shown here. It was not felt appropriate by these investigators or their ethics committee that it would be ethical to randomize these patients to an alternative treatment, and hence, they were open, uncontrolled studies.

And these are the eight sites where the separate study was conducted in Australia.

This shows the flow-through diagram that you've seen before. In these two studies, the 205 study consisted of 94 patients with 123 BCC lesions, and the 310 study, 102 patients with 165 lesions, making 196 patients altogether.

Now, the definition of high-risk BCCs in this trial, as you know, did not include the morpheaform or multi-focal, micro-nodular BCCs, but it did include in the 205 study large basal cell carcinomas which was defined in this instance as being greater than 20 millimeters on the extremities compared with 15 millimeters on the extremities in the 310 study; greater than 30 millimeters on the trunk in the 205 study and greater than 20 millimeters on the trunk in the 310 study; and the same size, greater than 15 millimeters on the face.

Both studies included BCC lesions located in the mid-face defined as the nose, nasolabial fold, and orbital area, or ear in the 205 study and similarly in the Australian study, including Swanson's described H-zone, which includes the temple.

In the European study, recurrent BCCs were included, and they were defined as a treatment failure after two previous treatment within a year. In the Australian study, we included a group of patients at high risk for surgical complications, and these were patients who may not have been able to have surgery because of bleeding problems, patients on anticoagulant medications such as warfarin, or were unsuitable for surgery for other medical reasons.

In the 205 study, there was a subgroup of

patients who were severely sun-damaged and it was felt that surgery and radiation therapy was not a good option for those patients due to their frequent recurrence.

Although these pictures do not depict all our patients, they're just to give you a flavor of the types of patients that were included. In the 205 study these patients have central facial lesions, here on the forehead, the tip of the nose, a young woman with one above the lip, and one behind the ear. There was a large group of patients with multiple superficial basal cell carcinomas such as this man on the trunk and this woman with the superpubic lesion here. And this is an example of a couple of the severely sun-damaged patients. I believe this woman had at least 10 lesions included in the study, and this man, who has had lots of previous surgery, who had a new BCC on his cheek here.

In the 310 study in Australia, we also had H-zone lesion patients. This is one of my patients here, a young woman with a BCC on the temple and another young woman with one on the nose.

In the 310 Australian study, we also included quite a number of patients with large BCCs below the knee. As we all know, this presents surgical problems from the point of view of primary excision and closure because you don't get lots of excess skin on your lower legs, and also

circulation problems. These lesions often have to be treated with grafts and flap surgery. This is one of my patients who was diabetic and elderly, an 80-year-old woman with a large BCC on her lower leg with peripheral vascular problems, and another one of my patients who had AIDS and hepatitis B who had a large nodular BCC on the dorsal of his foot.

So having said that, the study protocol was similar to the ones you've just heard about. The patients had two sessions, one treatment cycle, 7 days apart, as you've heard. Then they had an assessment performed at 3 months in which, if it was clinically felt they had had an incomplete response, they then went and had another MAL-PDT cycle of two sessions again. However, if it looked as if they had complete response, then they had biopsies taken, which I will explain to you in a moment, and as long as those biopsies were clear, these patients are being followed annually for 5 years. These patients who underwent two treatment cycles 3 months after the last treatment cycle had the same assessment, and if it was complete on biopsies, they went into the 5-year follow-up group. And those patients where the biopsies showed there was still BCC present went on to alternative treatments and had to drop out of the study.

This shows the type of assessment that was done

at the 3-month period after the last PDT treatment, and patients, in addition to having body maps done, of course, and templates to mark out the lesions, if they were large lesions, had this stamp put over the lesions, and in the 310 study, a 2 millimeter punch biopsies was taken from every square millimeter of that stamping area. In the 205 study, one biopsy was taken per lesion from the clinically most suspicious part of the lesion.

In addition, in the 205 study, they had an independent reviewer who reviewed photographs and histology reports from the lesion at the point where the patient was recruited. This reviewer excluded 9 patients after going through this process in this study. In addition, the independent reviewer reviewed the cosmetic outcome and response on pathology 3 months after the last PDT treatment.

Now, to the results of these studies. This shows the percentage of lesions by patient, and you see that in both studies the majority of patients had 1 lesion, especially in the 205 study. In the 310 study, 19 percent had 2 lesions.

This bar graph shows the percentage of patients having different types of BCC lesions. In the 205 study, there was an equal distribution between superficial and nodular types of BCCs, and as expected, the majority of the

nodular lesions were on the face and scalp shown in red. In the 310 study, there was 50 percent of lesions which were superficial, and the other 50 percent was equally divided between nodular lesions and mixed nodular/superficial types. Typically most superficial BCCs were on the trunk.

The size of the lesions was similar between the two studies: 23 millimeters for 205 and almost 20 millimeters for the 310 study.

The distribution of the types of high-risk lesions included was similar in that the large lesions comprised about 50 percent of both studies: the mid-face lesions, a higher proportion, 43 percent in the 205 study; 29 percent, H-zone lesions in the 310 study.

In the 205 study, 13 percent of lesions were recurrent, defined as two recurrences within 1 year. Surgical risk only patients comprised 16 percent of the 310 study patients, and 15 percent of these study patients were the severely sun-damaged patients.

This is our primary efficacy endpoint result by patient. So every patient had to have all of their lesions completely responding and by intention-to-treat analysis at 3 months after the last PDT treatment. In the 205 study, it was a 72 percent response by patient, and in the 310 study, an 80 percent response.

This shows for the 310 study the results broken down by type of high-risk category, and you'll see that the patients at high risk because they were unable to undergo surgery had a 100 percent response, and the other high-risk subgroups had similar response rates in the low 80s.

The lesional complete response rates, which we would expect to be higher, by intention-to-treat analysis in the 205 study was 75 percent and in the 310 study 85 percent. The cosmetic outcome was graded in the 205 study by the investigators and the independent reviewer and found to be good to excellent in most cases, and in the 310 study, by the investigator and the patient, and again found to be good to excellent, with higher ratings by the patient.

These are these life tables again, the time to event tables. The pink line shows you the results for the 205 study going out to 36 months, and the blue line, the 310 study, going out to 24 months, 2 years. These numbers just give you an idea of the numbers of lesions that were present at the beginning of the study and that are being followed currently. So that gives you a good idea of the treatment failures at the beginning and then the recurrences that are developing with time.

So, in conclusion, from these two uncontrolled studies, the 205 and 310, in this definition of high-risk

BCC we see some supportive evidence of efficacy and especially utility in some patients with these types of high-risk superficial and nodular BCCs. I believe that MAL-PDT offers an alternative treatment -- not a primary treatment, an alternative treatment -- for BCCs when Mohs might not be the usually used or preferred treatment. Such examples might include some of these multiple large superficial BCCs, patients with lower leg lesions, and patients with medical contraindications for the use of surgery.

In addition, the studies demonstrate good to excellent cosmetic outcome in patients with central facial and ear lesions and large superficial BCCs.

Now, we will have the important presentation on the safety results from all of our studies by Dr. John Posner.

DR. POSNER: Thank you. Good morning, ladies and gentlemen. My name is John Posner. My background is internal medicine and clinical pharmacology in the pharmaceutical industry, and I've been working as a consultant independently with PhotoCure now for the last five years.

I'm going to present the safety data on the BCC and AK population, the total experience that we have with this product. I'll start with some definitions and

methodology, describe the safety patient population, the adverse events, a brief word about clinical laboratory data, and finally the important subject of irritancy and sensitization.

Adverse events and serious adverse events were defined in accordance with the ICH guidelines on good clinical practice.

To err on the side of caution, treatment related were considered all those that are classified by the clinicians as yes or uncertain.

The period of recording is important to note. They were different for actinic keratosis lesions where the period of recording was confined to 3 months after the last treatment, that is to say, when the final assessment was done; whereas with the basal cell lesions, it went from the randomization to 6 months for all adverse events and then continuing during the whole of the recurrence period for serious adverse events which, of course, includes deaths. Currently we're just coming up to 3 years. In some trials we're there and some we're not quite there.

The coding I'll say a word about in a moment when we look at the non-local adverse events, but essentially local adverse events are those applying, according to the WHO classification systems of system organ classes, to skin and appendages. There are some terms that

are not in the dictionary like bleeding skin, tingling skin, and pain in the skin that were added by the sponsor. The non-local adverse events are all those adverse events relating to other system organ classes.

The population then. We have clinical trials in basal cell carcinoma, which you've heard about, of 538 patients. That also includes the early phase I/II studies with a relatively small number of patients. Clinical trials in actinic keratosis here as 383 patients, compassionate use of over 1,000 patients, and some post-marketing experience currently up to about 35,000 patients.

Most of what I'm going to be talking about, of course, is the clinical trial population, and here the clinical trial safety population is the same as the intent-to-treat, which is all patients randomized to treatment who received at least one dose of the randomized medication or who underwent at least one of the other interventions.

All the MAL-PDT patients in BCC are mentioned here, 538 patients with 857 lesions and over 1,600 PDT sessions because, of course, many of them had two or more sessions. In addition, we have these 383 AK patients, but because of the number of patients with multiple lesions, we actually have over 2,000 PDT sessions here, and the total comes to nearly 4,000 sessions of MAL-PDT.

Now, the number of clinical patients in

clinical trials with treatment emergent adverse events. Here you see the 538 BCC patients, and about 80 percent of the patients had adverse events. As you can see from the breakdown, 75 percent of those, three-quarters of those, were local adverse events, and 27 percent are classified as non-local. In AK, actually the profile is very, very similar: 74 percent local and 22 percent non-local.

The deaths and serious adverse events. In the BCC population, we have 18 deaths and we have, in terms of serious adverse events, about a 5 percent rate here. None of the deaths and none of the serious adverse events, with the exception of one, were considered to be treatment-related and they certainly weren't local.

This one local serious adverse event was a patient who had severe pain at the time of illumination and the patient required admitting to hospital, and for that reason was considered a serious adverse event. The patient received analgesia. The pain subsided and he went home the next day.

You'll notice that the death rate here, the mortality on the BCC, is considerably higher than that with AK. This simply reflects the duration of follow-up. Here we're talking about elderly patients being followed for 3 years and inevitably there will be deaths. We've obviously looked very carefully at all of these and there isn't

anything that is even vaguely treatment-related there. AK was a much shorter period of follow-up.

The non-local adverse events. So these are not the serious ones, but they are classified as non-local. I want to make the point that there is very little evidence of systemic adverse events. In fact, the commonest cause for a non-local adverse event was a basal cell carcinoma discovered at another site. This was coded, according to the system, as a neoplasm and, therefore, because it didn't fall under skin and appendages, got classified as a non-local adverse event. Clearly it's not systemic.

The same applied to surgical intervention for a preexisting skin lesion. So the surgical intervention in that case went down as a non-local adverse event.

If one then removes those, because they're not systemic, one is left with a variety of individual symptoms as you would expect, influenza-like symptoms, occasional reports of headache, and then even more occasional dizziness or blurred vision. I should point out any reports of blurred vision we've looked into carefully. They were not local to the site of treatment.

So our conclusion from careful scrutiny of these non-local adverse events is that in fact there's no evidence of systemic effects of this treatment.

Now to the local adverse events, and the vast

majority of these were treatment-related. They come under really this complex of symptoms and signs which we call phototoxicity. Typically it is pain or discomfort at the site of illumination on treatment. The pain is often described as burning or stinging, and also the other most common adverse event of this nature that goes into the phototoxic complex is erythema, almost invariable. Edema of the skin is also frequent.

If we look at the profile of the relative incidence of these for the total population of BCC and AK, we're talking about erythema being the most frequent. Pain in the skin, burning skin, we also have stinging skin there, the edema, local pruritus, crusting, blisters, suppuration. And this goes down to the 5 percent level. You have a more complete table in your briefing document that goes down to the 1 percent level.

I should point out that the numbers are quite inflated here because if a single patient said that they had pain and they also said that they had burning and stinging, that went down as three separate adverse events which were all rated.

The severity. The majority of them are mild or moderate, but we do have some patients, averaging about 10 percent, which are classified as severe. This was usually pain. So 1 in 10 patients approximately will have

complaint of severe pain beginning at the time of illumination and subsiding rapidly afterwards. There was no difference in any of these between the basal cell carcinoma and the actinic keratosis populations.

Despite this high incidence of phototoxic adverse events, the discontinuations really were few and far between. In the basal cell population, we just have .7 percent actually discontinuing, and AK, just slightly more than that, an average of 1 percent withdrawals.

The duration of the local adverse events. Skin pain, burning, stinging, tingling, as I say, generally starts at the time of illumination and then subsides over the next few hours, and the median time is less than 1 day, so generally on the day of treatment, subsiding rapidly.

Edema and other inflammatory signs you see listed here typically lasts for a few days up to 1 week, and erythema and crusting, as you would expect, skin ulceration occasionally, suppuration infection in about 1 percent of patients generally resolve within a couple of weeks.

We were interested to know if the number of local adverse events, phototoxicity, increased or decreased with the number of sessions that the patient receives. So we've broken this down by the number of sessions and the incidence of local adverse events in this BCC population.

So here we see 250 patients who received two sessions. In fact, we find that the incidence of phototoxic adverse events decreases. Here we have 94 patients who had four sessions and we see that it's actually declined pretty well from at least the third session of PDT. So we can say that there's certainly no increase in the number or the severity of adverse events with repeated application.

Looking at the comparative data -- and, of course, although these studies were powered adequately for efficacy endpoints, they are small in terms of safety. But if we look at the difference between the MAL-PDT and the placebo or vehicle-PDT groups, in this particular population, we do see a difference, the typical 74 percent here for the MAL-PDT, but almost half the patients receiving the placebo or vehicle treatment also had local adverse events, no doubt reflecting the preparation, cream application, illumination procedures.

In terms of non-local adverse events, the percentages here are slightly higher in the MAL-PDT but very few of these, four cases, were considered to be related here and two there. So the vast majority of these are not considered to be treatment-related.

The severity: mild, 47 percent; moderate, 53 percent; no severe here in the MAL-PDT. The placebo really

rather similar.

The results in comparison with surgery are confounded by the fact that all the patients who had surgery had local anesthesia, whereas those with MAL-PDT did not. So it's really rather difficult to interpret these results, but what we can say is that under the local anesthetic, the surgery incidence of local adverse events is 16 percent versus the MAL-PDT of 50 percent not under local anesthetic. No difference in the number of non-local adverse events. Here the severity, all of the surgical ones were mild.

Cryotherapy. The results in terms of adverse events and particularly local adverse events are very similar with MAL-PDT and the cryotherapy, 70 percent, 78 percent; and non-local here, 28 percent, 36 percent, the vast majority again not being considered to be treatment-related. The severity of these is rather similar for the two treatment modalities.

Those are the clinical trial data. We then have the compassionate use study in which just over 1,000 patients were treated in Norway, mostly at the Norwegian Radium Hospital, but also in some other centers. These were patients with a variety of lesions, mostly BCC, and nearly 1,500 AK lesions and some other non-melanoma skin cancers. There was no formal GCP here, good clinical

practice, as performed in clinical trials, but there was some collection of solicited data on pain and erythema, and the outcome essentially is in line with the clinical trials, that the majority of patients have pain and erythema, but there were very few non-local adverse events.

We do have some post-marketing experience. The product was launched initially in October 2001 in Sweden, and in the last year and particularly in the last few months, we have the UK and Germany coming on stream, plus three other Nordic countries. So by June of this year, we have some experience of an estimated 35,000 patients which probably represents certainly over 50,000, maybe as many as 70,000, PDT sessions.

These are the spontaneous adverse reports that have come into the company either through the regulatory authorities or directly. Most of them are fairly unremarkable, but I would like to mention these two classified as eczema by the clinicians.

One of these was considered to be an allergic response, but no patch test was done, and the description of the symptoms and signs are, in fact, completely compatible with phototoxicity. It's really very difficult to distinguish that. So we don't know whether that was a case of sensitization.

The other case has been more thoroughly

explored. It was a patient with diabetic necrobiosis lipoidica on the lower legs and had several treatments with MAL for this condition. The patient developed an allergic response after several treatments with some blisters, and the patient was rechallenged with MAL and with ALA some weeks later. The patient was positive to a skin patch test to MAL but not to ALA. Actually at the very highest concentration of ALA, 10 percent, there was a very weak response. Essentially it was a positive skin patch test. And that is the only definite case, confirmed case, of sensitization that we can refer to.

We'll come back to the question of sensitization in a moment, but just a word about clinical laboratory data. As has been said, we are confident that the absorption of this drug is minimal, and so we do not expect to see adverse events of a systemic nature. But nevertheless, we've monitored clinical laboratory data in the phase I and II studies, a total of some 375 patients, and in particular concentrated on liver function tests because the target organ toxicity at concentrations many thousand times more than at which a patient would be exposed systemically was the liver.

To cut a long story short, what we can say is that there was a completely uniform distribution, quite random, of changes in liver function in terms of

transaminases and bilirubin, with no patient actually having more than a twofold increase over their baseline value after treatment, and the vast majority of patients actually having a change of less than 40 percent. Normally one clinically thinks of times 2 or times 3 the upper limit of normal, and none of the patients showed this sort of increase. There were, of course, a few patients just through random distribution above the upper limit of normal when they started and a few when they finished, but there was really no indication of any change here. And we conclude that there are no clinically relevant findings in liver function tests or other laboratory parameters, and for that reason, clinically laboratory tests were not monitored in the phase III studies.

Now, the question of irritancy and sensitization and cross-sensitization to 5-ALA. Two preliminary studies were done in healthy volunteers which suggested that there was no irritancy for a 24-hour exposure, but if you exposed for 2 weeks continuously, then you started to get an incidence of irritation, and when patch tests were done, there was an incidence of positives.

So a much larger study was set up, this study 110, in which it was intended to recruit over 200 subjects. These are all healthy volunteers, and 224 were screened, but in fact because they were in staggered groups, not all

of them entered. The last group was not actually entered into the induction period, and the reason for that was that it was quite clear that there was a high incidence of irritancy and it was felt that it would be inappropriate to just recruit and put in another cohort.

156 subjects had a 3-week application of MAL and its vehicle on the upper back. MAL and the vehicle cream were applied 3 times a week, so a total of 9 times during the induction period under Finn chambers and tape occlusion continuously. They did not have any illumination, and there was no rest period. At the end of the 3-week induction, they then had a 2-week rest period, followed by a challenge on the arm with MAL or its vehicle or 5-ALA and its vehicle.

Because of the high incidence of irritancy, in fact a number of volunteers by mutual agreement with the investigator, who was Professor Ronald Marks in the UK who is a specialist in this area, it was agreed not to challenge them all with the MAL. So actually 58 subjects had the MAL and the ALA challenge and 40 just had the ALA or vehicle. Then the challenges were read over a course of 48 hours.

All but 1 subject reacted with erythema during the 3-week induction period to MAL. The earliest reaction of moderate severity, a grade 2, occurred after 4 days of

constant exposure, nothing before that. There was very little reaction observed on sites exposed to vehicle.

Sensitization on patch testing of the 58 subjects that were challenged with MAL, 52 percent had clearly positive reactions with MAL and just 1 subject with the vehicle, and of the total 98 subjects who were challenged with ALA, there were no positive responses. This is very important because, of course, ALA is an endogenous material.

The conclusion then is that there is no doubt that MAL can cause irritation and contact sensitization, but there's no evidence of cross-sensitization to 5-ALA.

We do question the relevance of these findings. Sensitization in clinical practice has been rare, with just the one confirmed case that I've described and no other confirmed cases in the clinical trial population. This one confirmed was from the post-marketing experience. The conditions in clinical practice are really very different. We have a short exposure, 3 hours versus 3 weeks continuous, and we don't see any irritancy due to the cream before illumination. Of course, irritancy is strongly associated with sensitization.

The illumination that is carried out in the normal clinical procedure after 3 hours results in photobleaching and, of course, phototoxicity. The

photobleaching means that the photoactive porphyrins have all been destroyed, which is an important feature of the safety, we feel, of this treatment, and the phototoxic reaction probably has an influence on the possibility of any immunological response, though that is of course speculative.

Finally, the occlusive dressing was different, Tegaderm versus an aluminum Finn chamber and opaque adhesive tape. We can't say how important that is.

So to summarize our overall safety conclusions, we've got experience in clinical trials of over 900 patients, compassionate use in over 1,000 patients, and post-marketing data from certainly more than 35,000 patients. We have no clear evidence of systemic effects of MAL-PDT. It does not cause generalized photosensitivity, and it's very well tolerated despite the frequent local phototoxic reactions with just the 1 percent incidence of discontinuation in our trials.

MAL can cause local irritation and contact sensitization, but this was in a very intensified and prolonged exposure. Importantly though, despite that, there was no cross-sensitivity to ALA. And definite cases of sensitization in clinical practice appear to be rare. There's only one confirmed case in the post-marketing.

Thank you, and I'll now hand you back to Dr.

Hestdal to sum up the perception of benefit-risk.

DR. HESTDAL: So I will then try to conclude and close the session, and I've been asked to discuss this benefit-to-risk ratio of MAL-PDT in treatment of BCC based on the data that we have presented this morning.

This slide summarizes the demonstrated benefits of MAL-PDT. Safety and efficacy have been established in two vehicle-controlled studies based on histological endpoints. We have shown that initial and sustained response rates were similar to cryotherapy through 3 years of follow-up, and a favorable safety profile has been established in clinical trials as well as through post-marketing experience. Cosmetic outcome, judged both by the investigators as well as the patients, is superior to that of cryotherapy and excisional surgery.

The risks of MAL-PDT that we have discussed is manifold. Firstly, MAL-PDT was shown to give a smaller initial response and lower sustained response rate compared to surgery after treatment of nodular BCC. However, our histology data shows that there is a retained ability to treat with other modalities in the case of treatment failures.

Secondly, treatment success of MAL-PDT may require a second course of treatment at 3 months in some individuals. However, our data also show a similar rate of

retreatment with cryotherapy. In addition, BCC treatment guidelines already incorporate follow-up after other treatment modalities.

There is an indication of mild to moderate local phototoxic reactions. However, very few patients withdrew due to these phototoxic reactions.

Lastly, skin sensitization potential has been shown on the basis of special studies with very prolonged and extreme conditions. However, low rates are expected in clinical use based on the clinical trial and post-marketing data.

Therefore, in conclusion, MAL-PDT is a new and unique non-surgical treatment option for BCC with a favorable benefit-to-risk. We strongly think that this should be indicated for treatment of nodular and superficial BCC where surgery is not desirable.

In that way, I will thank you and this is the end of the presentation on behalf of PhotoCure. I will thank you very much.

DR. STERN: Thank you very much for your presentations.

Because the presentations went over, I would prefer if we only ask questions of clarification before the break and then went on to the FDA. There will be plenty of time for longer questions. So let me give three examples

of questions for clarification that I have.

It's my understanding that the application is for the treatment of superficial and nodular basal cell and not for high-risk lesions that's before the agency. These are questions that I hope would be yes/no or it's this or that. Is that correct?

DR. HESTDAL: Could you please repeat?

DR. STERN: Does your application include the treatment of high-risk lesions? Yes or no.

DR. MORRIS: Yes.

DR. STERN: The application before the agency includes as an indication the treatment of high-risk basal cells?

DR. MORRIS: No.

DR. STERN: No. Okay, thank you.

DR. MORRIS: It includes data on that.

DR. STERN: Yes, but it does not include it in the application.

DR. MORRIS: No.

DR. STERN: These are all just simply that.

A procedural one, something about the procedure. Before the application of PDT at each of the sessions, was curette done again before applying the agent or was it only applied with the first time a patient was treated?

DR. MORRIS: Maybe we should let the clinician answer that.

DR. PARISER: The one-word answer is yes. Each session of PDT, curettage and lesion debulking is part of the treatment.

DR. STERN: My third -- just because the data weren't presented -- and maybe you should stay there -- is it looks to me, from the data presented, that somewhere between one-third and one-half of patients in the studies had at least three PDT treatments. Is that correct?

DR. MORRIS: Yes, about one-third needed a retreatment. Yes.

DR. STERN: Thank you.

Any other questions of clarification of that sort of yes/no, what did you do, as opposed to the data and what it means? Yes.

DR. KATZ: Of the lesions in the H-zone, what was the size of those lesions? That was not enumerated. You told us on the superficial ones. Do you have that?

DR. MURRELL: They could be small lesions, but I believe some of those lesions were large lesions.

DR. KATZ: There were no limits on size.

DR. MURRELL: That's what I recall.

DR. KATZ: The other question is what was done for the bleeding after the curettage. Some styptic or you

had a little bleeding there?

DR. MURRELL: There was a little bit of bleeding but we never needed to use cautery for that.

DR. KATZ: Just pressure?

DR. MURRELL: Yes, pressure and when you put the cream on, sometimes there was a bit of blood mixed in with the cream under the dressing.

DR. KATZ: But no cautery was done, no styptic.

DR. MURRELL: No.

DR. KATZ: Thank you.

DR. DRAKE: Two quick questions. On the cryosurgery, did you use a temperature probe or was it just all visual inspection?

DR. PARISER: It was visual inspection.

DR. DRAKE: Second question. I should know this but how deep does the light penetrate?

DR. HANSSON: We actually have a slide of that on the various blue light, green light, red light. Red light penetrates at this wavelength where you don't have any quenching by heme far into the dermis. So the light penetration has no limitation for the treatment effect.

DR. DRAKE: I actually would respectfully ask you to -- we can do it after the break, but I'd like you maybe to consult because I don't think you can say there's no limitation to how deep light goes. There are clearly

measures of each wavelength about how deep they'll go. So if you could clarify that a little more for me after the break, I would appreciate that. Thank you.

DR. RINGEL: I understand that for studies 307 and 308 excisions were done after the tattooing and after the treatments had occurred. What were the margins taken around the tattoos, or were only the tattooed areas excised?

DR. PARISER: Well, the tattoos were placed just beyond the visual margins of the lesions, and the excisions were taken to include the tattoos. It was not prescribed. 3 millimeters from the lesion and the tattoo was placed on the edge of the lesion and the excision was 3 millimeters from the lesion. Where the tattoo was in relation to that was not prescribed by the protocol.

DR. RINGEL: The lesion has completely disappeared because this is a complete response. So all you see is the tattoo. Was there a margin taken around the tattoo, and if so, how much?

DR. PARISER: Well, 3 millimeters. It was assumed that the tattoo was placed at the edge of the lesion. So when the patient came back and was responding, the 3 millimeters from that included the tattoo.

DR. STERN: Dr. Plott?

DR. PLOTT: My question is similar. Was there

any attempt to characterize the recurrent to incomplete responses after they were excised?

DR. PARISER: In what way? The histologic type of the lesion or --

DR. PLOTT: To look at was it more aggressive or any characterization --

DR. PARISER: We can ask Dr. Gibson, the pathologist, to comment about that.

DR. PLOTT: Well, just yes or no.

DR. PARISER: There was no change in the lesion. We didn't convert any nodulars to morpheaform basal cells.

DR. TAN: So in the vehicle arm, did you use a placebo cream? What kind of light was used?

DR. PARISER: Well, the vehicle treatment was the exact same cream in the placebo without the active ingredient and the illumination was the exact same illumination. So the placebo treatment, as we defined it, consists of the application of the vehicle cream without the active ingredient, the application of the occlusion for 3 hours, and the same illumination as was carried out with the active.

DR. TAN: Illumination is the same.

DR. PARISER: Yes, correct.

DR. STERN: But clearly you're not calling

these blinded studies.

DR. MORRIS: Yes.

DR. STERN: I don't know how you can call it a blinded study when at least 75 percent of the people get stinging and burning, if not 100 percent, with the agent.

DR. PARISER: Well, the investigator and evaluator of the lesions was not present at the time of the treatment and --

DR. STERN: It's not patient-blinded at least.

DR. PARISER: Correct.

DR. STERN: Okay.

DR. PARISER: However, some patients on placebo did get a similar response.

DR. KING: To begin to frame the question that Dr. Wilkin asked about writing kinds of input for the PDR, generally when you think about surgery and cryosurgery, et cetera, you think about exclusionary kinds of things. If you have somebody who has a tendency with cryoglobulin for cryosurgery, that would be a complication or bleeding in blade surgery.

What did you do to exclude patients who may have undue phototoxic responses or indeed may have porphyria? I didn't see anything about what are contraindications in the whole description here. So you're saying basically there are no contraindications.

DR. PARISER: That was an exclusion criteria with porphyrias. Some natural porphyrins are present in the skin which may account for some of the placebo response in this.

DR. STERN: Any more clarification questions?

(No response.)

DR. STERN: Then we'll have a 16-minute recess and be back at 10:20. Thank you.

(Recess.)

DR. STERN: I'd like to reconvene the meeting with the beginning of the FDA presentation on the application for MAL-PDT for superficial and nodular basal cell cancer.

DR. VAUGHAN: Good morning, Mr. Chairman. Good morning, members of the advisory committee, invited guests, and attendees.

NDA 21-576 is being reviewed for the use of methyl aminolevulinate cream, or MAL, sometimes referred to as methyl ALA, with curettage and photodynamic therapy -- I'll be referring to that as PDT -- for the treatment of basal cell carcinoma.

The FDA clinical and statistical review team consists of the medical review team: Dr. Markham C. Luke, dermatology team leader; myself; Dr. Brenda Vaughan, medical officer. The statistical review team consists of

Dr. Shiowjen Lee, who is on leave, and Dr. Mohamed Alosh, the statistical team leader, who will be presenting today.

Curette-MAL-PDT is a drug/device combination, the physical and the chemical. It is a drug/device combination, and it consists, as you have seen, of lesion preparation, of curettage, application of MAL cream under occlusion for 3 hours, cream removal, and illumination with the CureLight lamp. Although the device is reviewed by the Center for Devices and Radiological Health, the device is an integral part of the application for this drug for treatment of basal cell carcinoma.

Now, you've heard some discussion this morning about results in primary superficial BCC. The agency agreed that one independent multi-center, randomized, active-controlled study conducted in patients with primary basal cell carcinoma might be acceptable depending upon evidence of safety and efficacy being established for the nodular BCC indication. Therefore, the comments that I will be presenting today will focus on the primary nodular basal cell carcinoma indication.

It has been established that curette-MAL-PDT is statistically superior to curette-vehicle-PDT in the treatment of primary nodular basal cell carcinoma. The issues that we would like for the committee to consider and discuss today are the adequacy of these studies. You will

be asked to consider the adequacy of the studies for estimating the cure rates with use of MAL cream based on early histology of the physical studies and the small number of patients that were enrolled in these studies, also the minimal recurrence data available for nodular BCC.

You will also be asked to discuss and consider the adequacy of instructions of lesion preparation, and Dr. Alosh will discuss the apparently high vehicle-PDT response rate and the wide center-to-center variability.

Since this is a skin cancer, we're going to ask you to consider the estimate of cure rate for MAL-PDT versus surgery, which we consider the gold standard.

From the data that have been submitted, there does not appear to be a systemic safety signal based on the laboratory and reports of non-local adverse events. However, we will ask you to consider the local safety surrounding pain and the minimal information provided regarding anesthesia and pain control and an unusually high contact sensitization to MAL cream.

Measurements of efficacy. The agency proposed that efficacy be based on clinical observation and excision histology and that 5-year recurrence rate data be presented. We agreed that 2-year data would be acceptable for filing of the NDA. PhotoCure submitted the pivotal studies based on excision histology alone, other studies

based on clinical observation alone, and recurrence rates based on clinical observation.

Studies that were interpreted for efficacy by the agency for the primary nodular indication were two vehicle-controlled randomized studies, 307 and 308; one open-label randomized MAL-PDT versus surgery for recurrence rates. But we also looked at a phase II open-label, non-randomized MAL-PDT study for recurrence rates which also had superficial patients enrolled, and I'll speak about the problems we have with including this study for the recurrence rates.

The pivotal studies were two studies conducted, one in the U.S., one in Australia. Study 307 in the U.S. enrolled only 33 patients randomized to the curette-MAL-PDT study arm and 32 patients randomized to the curette-PDT group. The study in Australia also had only 33 patients randomized to curette-MAL-PDT and 33 patients randomized to the vehicle group.

I'd like to draw your attention to the study design and thank the sponsor also for mapping out the design because it is complex. The study design consists that patients would receive either one or two treatment cycles. The first treatment cycle consisted of two curette-MAL or vehicle-PDT treatment. Treatments were to be identical, conducted 7 days apart, and followed by

clinical assessment at 3 months. If there was a partial response to the first treatment, then a second treatment, identical cycle, would be repeated with two additional PDT sessions conducted 7 days apart.

The pivotal study designs were as follows. At the 3-month clinical evaluation, this was the time to determine further management. If the lesion were in complete response, in other words, complete disappearance of the lesion, the lesion was followed and excised for histology at 6 months. If there were a partial response where the lesion was decreased by equal to or greater than 50 percent, then a second PDT cycle was administered. The lesion was followed and excised at 9 months for histology. If there was no response, that is, if the lesion were decreased by less than 50 percent, or if there was progression, the lesion was excised at the 3 months. I want to point out that complete response is not equal to cure for a basal cell in this study design.

So to review again, there's randomization to MAL or vehicle-PDT. There's the first treatment cycle and there were two PDT, curette-MAL-PDT, or vehicle treatment sessions conducted 7 days apart.

At the 3-month clinical evaluation, if there were a complete clinical response, the lesion was followed for an additional 3 months and excised at that time point.

If there was no clinical response -- but this group also included those patients with the partial response that was less than 50 percent -- the lesion was excised.

Those in partial response whose lesion had been decreased in size by at least 50 percent received a second treatment cycle, conducted 7 days apart.

At the 3-month clinical evaluation, following the second treatment cycle, those lesions in complete response were then followed again for 3 months and then excised.

If those lesions at this evaluation point with an incomplete clinical response, these lesions were excised. So, therefore, at the end of the pivotal studies 307 and 308, all lesions had been excised.

Dr. Mohamed Alosh will discuss the statistical analysis of the pivotal studies.

DR. ALOSH: Good morning. Thank you, Dr. Vaughan.

To discuss the efficacy results briefly, I'll be touching an analysis unit as well as the criteria for assessing the efficacy.

First, as some of the patients could have more than 1 lesion, as you are aware, we could speak about the lesion response rate or the patient complete response rate.

For the purpose of the submission, the patient complete response rate was the primary analysis endpoint. The secondary endpoint was the lesion complete response rate.

The sponsor presented the results for histology alone, and the criteria for assessing the response was based on the agency recommendation that it's supposed to be clinical and histology. This was based on a recommendation in a meeting on March 7, 2000 with the sponsor.

In the protocol, PhotoCure reported the results for histology alone. The reason I bring this is because clinical and histology response rate would be a subset from histology. Consequently, the response rate for clinical and histology, you'd expect it to be lower as we'll see. I would like to repeat Dr. Vaughan's comment that complete response is not equal to cure.

We agree with the sponsor that curette-MAL-PDT is superior to curette-vehicle-PDT. We are concerned a little bit about the variability in the success rate estimate for MAL-PDT which might be attributed to relatively small studies, and this would lead to a wide confidence interval around the point estimate, as we'll discuss shortly.

Then also there is uncertainty about lesion preparation description. The clue for this, as you can see on the next slide, is we see high vehicle response rates in

this basal cell carcinoma, as well as there is center-to-center variability. Again, I'll repeat that these are small studies and the statistical findings should be interpreted with caution because some of the centers have less than 5 subjects per treatment arm.

So to talk about the apparent high vehicle response rate based on the sponsor-preferred analysis, based on histological evaluation, you can see here for study 307, you have in the curette-vehicle-PDT 39 lesions. Out of those, you have 13 lesions that ended up in complete success using histology alone. So you end up with a vehicle response rate of 33 percent. This is for the ITT population. If you consider the per-protocol population, you have a 35 percent response rate for the vehicle.

If you take the patient response, you can see similar results also for the vehicle. You can see out of the 32 patients, we have 11 of them successes. So the success rate for the vehicle is 34 percent. If you look to the per-protocol, they have similar results.

So about a one-third, roughly, response rate. Whether you look to the lesion response rate or the patient response rate, you have one-third roughly, the response rate for the vehicle.

If you look to study 308, the result is a little bit lower for the vehicle, but again it's also lower

for the active, with a difference of about 10 percent. I will touch on this briefly on the center-to-center variability. If you look again to the patient response rate, you could see about roughly 18-19 percent in this study. So you can see there is variability across the two studies, and the response rate, whether you consider the lesion response rate or the patient response rate, in particular for the vehicle which is very high. There's a question of whether histology is sensitive enough to assess the efficacy or there is the curettage doing something for the efficacy results.

In the next slide I'm going to briefly summarize the efficacy results if one considers the response rate for the clinical as well as histological evaluation. Here my focus is really on the point estimate of the response rate, i.e., the success rate. I'm not interested in the treatment effect because, as I said, we agree with the sponsor that it's effective.

So you can see for study 307, if you take the patient complete response rate, it's 73 percent, and the 95 confidence interval, this range. So the success rate could be as low as 54 percent for the active in study 307.

If you look to the success rate for the vehicle, it could be as high as 43 percent. We agree that they don't overlap because the p value is significant, but

we can see how much the range is.

Those point estimates, along with the confidence interval, should be kept in mind in terms of looking to the efficacy of other modalities such as surgery and the cryotherapy, which the sponsor presented the results from two European studies this morning.

Similarly, if we look to the lesion response rate, you can see for study 307 the lower 95 percent confidence interval could be as low as 52 percent. For the vehicle, the upper limit for the 95 percent confidence interval could be as high as 42 percent.

If you look to study 308, again the lower limit for the active could be as low as 45 percent; for the vehicle, it could be as high as 32 percent. Similarly for the lesion response rate.

I'm going to touch later on the center-to-center variability. The issue there is the sponsor presented the results for the first treatment cycle which show a high success rate, about 82 percent, even though we have seen the overall efficacy of about 76 percent. I would like to clarify some disagreement between the sponsor and the agency results here.

PhotoCure, in calculating the response rate for the first treatment cycle, excluded those subjects who went through the second treatment who were partial responders.

Anyway, this is not the definition of the rate which is the number of successes over the number exposed or treated in this example. So the number here in the denominator, 28, is only those people who were either a success or a failure, because those who went through the second treatment cycle are excluded.

Now, if we do the usual arithmetic, taking the number of successes over the total number treated, we'll have a success rate of 56 percent. Similarly, for the vehicle, we expect a drop. The drop is still from 30 percent to 23, but here you can see a big difference in this. And this is for the histological evaluation.

If you consider a clinical and histological evaluation, the first treatment cycle is supposed to be if you take the successes over the number treated, it would be 46 percent for the active and 18 percent for the vehicle. For study 308, the results are similar.

I think the point here, in terms of calculating those rates, one would prefer the usual analysis, to have the number of successes over the total number treated. Basically I think this study design one could argue that it's impossible. It's difficult to estimate the success rate for the first treatment cycle or the second treatment cycle.

The reason you cannot estimate the success rate

for the first or second treatment cycle is because the study design is really complex. The second treatment cycle is based on a clinical decision regarding the first treatment cycle outcome of partial response. Basically those who are partial responders for the first treatment cycle, if they stay in the trial without a second treatment, we do not know the number who will end up in success or failure. So we cannot separate for those partial responders what the contribution of the first or second treatment cycle is because they are given two treatment cycles and since no randomization before the second treatment cycle was carried out, it would be impossible, I think, to separate the effect of the first treatment cycle from the second treatment cycle. So this response rate by treatment cycle I think is difficult to put an emphasis on them in this study.

Having said that about estimating the response rate for the first treatment cycle, I still believe the data from the first treatment cycle could be very useful in looking to the center-by-treatment interaction. The reason for that first treatment cycle will contribute, will have the largest data set in which every subject has one treatment, and the majority of the patients are treated once.

On the next slide I'll be discussing the

efficacy results per center. Here we have seven centers in study 307. The first, second, and third columns give you the curette-MAL-PDT, the number of subjects in the denominator, as well as the numerator, which has the successes. And the third column is the same for the vehicle. You can see in this study center 30707 has 5 subjects in the active. All of them ended up in success. In comparison, we have 5 subjects in the vehicle. None of them ended up in success.

The point here, I think we agree the first treatment cycle is not the primary endpoint analysis. But, however, we are trying to explain the high response rate for the vehicle, and this in a clinical discussion, we have to look to this data and the first treatment cycle is appropriate here.

We have the Breslow-Day test for the first treatment cycle of .025, which is highly significant. If you consider the p value for testing interaction, it's .10.

Then we ran also the Zelen's exact test because you have a small number of subjects in every center, and you have .07. Again, it's significant at .1.

Now, here I have first and second treatment cycles combined in which you take the clinical and histological evaluation. You can see the Breslow-Day test is .13, and this is different than what the sponsor

presented, I believe about 26 or 30 because they used histological evaluation only while the agency recommendation was to have a clinical as well as a histological evaluation. In the last set of columns, we have it for the histological evaluation, which should be close to the sponsor, about 31 percent.

So to summarize, we have some concern about center-to-center variability for the first treatment cycle.

If we look to the second slide, here we have a similar analysis for study 308, which is the second pivotal study. We do not see in this study the center-to-center variability which we see in study 307. I would like to mention that those two extreme centers in 307, there is the efficacy result of the 307 by about 10 percent, and we remember there is difference in efficacy probably between the two studies, the 307 and the 308, of about 10 percent. So whether it's related with something else.

Here we run the Breslow-Day test. You can see there is no significant center-by-treatment interaction in study 308.

So in summary, we agree with the sponsor that curette-MAL-PDT is statistically superior to curette-vehicle-PDT for the treatment method used in the protocol.

For each study, there is a relatively high curette-vehicle response rate. There is also center-to-

center variability in study 307. This might be attributed to small study size with small centers. It might be attributed also to lesion preparation for treatment and to the accuracy of clinical and histological evaluations.

The center-to-center variability in the efficacy results reduces the reliability in the overall point estimates of curette-MAL-PDT.

Thank you. Dr. Vaughan will discuss further the curettage.

DR. VAUGHAN: Thank you, Dr. Alosh.

To review again, based on the protocol-guided outcome assessment, curette-MAL-PDT is statistically superior to curette-vehicle-PDT. However, the high response rates with the curette-vehicle-PDT, as indicated, was seen, and as touched upon by Dr. Alosh. The high rate in the curette-vehicle group may have been due to the effect of the extent and depth of curettage. It may have been due to the short-term follow-up of 3, 6, or 9 months, or it may have been due to a low ability to detect residual BCC by histological methods.

This is an example of a curette and lesion preparation provided by PhotoCure from the PhotoCure video.

Other factors in the pivotal studies appear to be consistent, such as lamp exposure, MAL cream application time, for each of the pivotal studies. Therefore, we think

that the response may depend on the extent and depth of curettage. This was discussed by Dr. Alosh, that efficacy shows center dependence and there was a high curette-vehicle-PDT response.

This is an example of curettage, of lesion preparation provided in your briefing package by PhotoCure on page 124. This patient, however, was not studied in the pivotal studies, not in studies 307 or 308. It appears from the photograph here that the lesion preparation appears rather extensive. During conduct of the clinical trials, most patients did not receive local anesthetics. However, according to concomitant medications for this patient, Xylocaine spray and Xylocaine was listed as a concomitant medication, but I'm not sure at what point or when any of that medication was used.

Recurrence data is a part of efficacy for the treatment of basal cell carcinoma. In the context of discussing the pivotal studies, since all lesions would have been excised, the agency and PhotoCure discussed the recurrence data for nodular BCC. PhotoCure agreed to provide a minimum of 250 subjects to be submitted. We requested a 2-year follow-up at NDA submission and that patients be followed up 5 years post-treatment as a phase IV agreement.

What was submitted was PhotoCure provided 2-

year recurrence data on 46 patients with 47 lesions with primary nodular BCC treated with curette-MAL-PDT from a study that you've heard about, study 303, which was a phase III randomized, open-label study versus one surgical excision.

In an attempt to have a larger database, we also looked at study 205, which was a phase II non-randomized, open-label study that included both nodular -- there were 38 lesions and superficial lesions, 39 lesions. There were other patients, 3 or 4 lesions, considered nodular/superficial. However, the focus will be primarily on nodular BCC, and I will discuss later the problems that we find with including these patients with the database for the primary nodular.

Recurrence is based on clinical assessment, inspection and palpation, and in some cases confirmed by punch biopsy when the lesion is clinically positive for recurrence. Treated areas that were apparently clinically clear were not biopsied and are being followed.

Study 303 that you've heard about was a European randomized, open-label, multi-center study in 101 subjects. There were 52 patients randomized to the curette-MAL-PDT study arm and 49 patients randomized to the surgical treatment arm. The initial post-treatment assessment was at 3 months, and patients were followed 12

to 24 months for clinical recurrence.

The surgical excision study arm underwent one excision. As previously mentioned, the surgical excision margin was standardized at 5 millimeters. However, the range was from 1 to 5 millimeters, and I believe a mean of -- PhotoCure can give you that. I think it was a mean of somewhere around the neighborhood of 5. However, the histology indicating whether the borders -- whether there was involvement of the lesions with BCC cells was not submitted to the agency for review.

Additionally, we're using this for recurrence data. The recurrence data protocol was embedded in the original study protocol and the follow-up procedures are minimally described.

This patient was provided by PhotoCure on page 100 of your briefing document, and it is given as an example of complete response. This patient is problematic in that it is difficult sometimes to evaluate responses based on photographic data. For example, in the second photograph here, the distance is further away and there's a light shining here on the area. So it makes it difficult to really assess the area that was treated. Nonetheless, this patient does appear to have a clinical response and a relatively good cosmesis from the treatment.

This patient also represents problems with

early clinical assessment because this patient was discontinued 3 months after this evaluation with a recurrent lesion. This patient also presents a problem, and we'd like your discussion about how to handle recurrence data for discontinued patients and missing data.

Recurrence will be discussed in terms of lesion recurrence because some patients had more than 1 lesion, although some had 1 lesion. Also for study 205, some patients had both types of lesions, both nodular and superficial.

So we looked at the recurrence data in two different ways. We looked at recurrent lesions and for study 303, the MAL-PDT treated arm had 1 recurrence within 6 months and 3 -- and this is a little bit different from the sponsor right here, but they had 3 at 12 months. And for the 24-month recurrence, we have 4 lesions for a 9 percent recurrence rate.

If we look at the missing data, we have 12 additional lesions that were missing from the 24-month MAL arm. If we add the 12 to the 4 recurrences, we get a recurrence rate of 34 percent, and the confidence intervals are given here. So depending on how you handle the missing data, recurrence rates based on clinical observation can range from 9 percent up to 34 percent or as low as 2 percent and as high as 49 percent.

For the surgery treated arm, the recurrence data was assessed the same. At 6 months, there was no recurrence. At 12 months, there was 1 lesion missing, so we added that in. So that gave us a 2 percent recurrence rate. So at 24 months, the recurrence rate for the surgical arm was 2 percent, and if we added the missing data, there were 7 lesions missing. Added to the 1 recurrence, it gives us a total of 16 percent. So for the surgical treatment arm, depending on how you handle the missing data, you can have recurrence rates from either 0 percent or up to 29 percent.

We also looked at a failure-to-cure analysis. For failure-to-cure, we looked at the initial failures to treatment, or treatment failures, plus recurrences, and then we added in the missing data, depending on how you want to handle the missing data. At 6 months, there were 9 out of 56 -- we're still talking about lesions here -- 16 percent. At the 12-month follow-up, there were an additional 12 missing lesions which gives us 21 percent. And if we add in the recurrent lesions of the 4 from the recurrence data, we can get a failure-to-cure rate of up to 45 percent, with a confidence interval of 31 to 59 percent.

The same approach was taken for the surgical treatment arm, and there was a failure-to-cure over the total number of lesions. At 24 months, including the

missing data, the recurrence rate for surgery may have been up to 16 percent.

The phase II recurrence study 205 was a non-randomized, open-label study that included both nodular and superficial BCC patients. This study included 57 patients with 79 lesions. They were evaluated for recurrence up to 24 months. The sponsor presented additional recurrence data that we have not had an opportunity yet to review for these patients presented today.

There were 30 patients in this group with 38 nodular BCC lesions, and there were also 3 patients with 1 superficial/nodular lesion with 1 lesion in the study. So there was recurrence data submitted at 6, 12, and 24 months.

However, we have difficulty including these patients in with the primary nodular in that the patient population was different. It was mentioned that the criteria that was used for consideration of high-risk, and it was also mentioned that one of the high-risk lesions, morpheaform, BCC was not included in this patient population.

The written instructions were different, appearing to have curetting below the epidermis.

There was a difference also in the application of the MAL cream to the lesion border. In the pivotal

studies, a 5-millimeter border was to be applied, but for this study, the border was listed as 10 millimeters.

Also, there were different lamps used in some patients. I think PhotoCure mentioned about 7 or 6 patients had used a different lamp. However, as I previously mentioned, the use of the lamp is an integral part of this application, and for patients with lesions that were 55 millimeters or above, up to 110, with use of a different lamp, it may not be applicable to the study of primary nodular. Also listed in one of the adverse events report, there was a second-degree burn listed for a patient who had received treatment, application of MAL cream and use of a different lamp.

However, we're presenting the data here for your consideration if you deem these patients should be considered in the recurrence data patients. For the agency's analysis with recurrent lesions plus missing lesions -- this is taken at 24 months, recurrence data. For superficial BCC, there was a 28 percent recurrence rate and the confidence intervals are given here, as little as 15 or as high as 45 percent.

But primarily we're interested in the nodular. The nodular rate was 37 percent. It could be as low as 22 or as high as 54 percent. And if you would like to include also the superficial/nodular patients, the numbers were

small and we have a 33 percent recurrence rate.

Now, one of the other difficulties with this study is that the study was non-randomized and the study was subject to a review board, therefore subjects and lesions were not included in the database. For example, the patients that I showed you with the curettage in study 205, with extensive curettage, there were a number of other lesions located on this patient. However, only the large lesion was included. In the superficial/nodular group, there was a patient who was followed out to 24 months and then discontinued from the study, stating that the patient should not have been enrolled, although the patient had had non-recurrence evaluations at 6 and 12 months.

So, in conclusion, the database consists of 46 patients or 79 patients, depending on whether you want to include the 30 patients from study 205 and the 3 patients with the nodular/superficial lesions. From study 303, there were only 46 with 2-year recurrence data.

The 2-year recurrence rate for MAL-PDT in patients ranged from 9 to 34 percent, depending on how missing data were accounted for, and the failure to treat adequately rate was 45 percent at 2 years. And a larger database was requested by the agency.

The cosmetic outcome has been assessed by PhotoCure, and in the pivotal studies, vehicle patients had

as good or a better cosmetic outcome than the MAL treatment group, but poorer response with regard to treatment outcome. However, the numbers were small.

Cosmetic outcome is considered secondary by the agency to non-recurrence of basal cell cancer. Recurrences may ultimately result in a worse cosmetic outcome due to the need for further treatment.

Assessment of cosmetic outcomes across treatments was not agreed upon between PhotoCure and the agency.

Data from the pivotal studies will be presented on the next slide. However, there are a limited number of patients in each study arm.

Photographic assessment was not provided to confirm the data. However, you have to be careful with photographic assessment, making sure that distance and lighting are as close as possible. The division did suggest or recommend that cosmetic assessments could be made prior to surgical excision in the pivotal studies and supported by blinded, independent review of photographs.

This is based on PhotoCure's results for the pivotal studies for the cosmetic outcome. However, in this study results are not consistent across the two pivotal studies. It was only the investigators in study 308 that rated the excellent response rates, when we're looking at

the excellent response rate, higher than the vehicle response rates. In the U.S. study, they were both about the same.

Patient assessment differed in the excellent category from the investigators in that the patients rated their cosmetic response rate higher than the investigator in the vehicle group in both studies. However, the results of their BCC being present was not known at this time.

As previously mentioned, there have been no systemic local effects identified from the adverse events reported and the laboratory monitoring. As PhotoCure pointed out, the adverse events were reported as local and non-local and that local did not mean treatment site reaction. It was not confined to treatment site reaction but was based on WHO classification of skin and appendages.

Someone had asked about blinding. In the pivotal studies, the investigators applied the cream and the study nurse applied the illumination to monitor blinding. The study nurses also recorded the adverse events.

The local adverse events that were reported were pain, burning, and stinging, and the phototoxic signs were erythema and edema. And there is a high contact sensitization rate. High contact sensitization has been demonstrated to MAL cream.

The local adverse events, as previously mentioned, consisted of skin pain, skin burning, skin stinging. The results are higher in the active group as opposed to the vehicle group. The sponsor has given you a summary of those adverse events.

Additionally, the adverse event severity was reported as moderate to mild in the pivotal studies.

The local adverse events in the open-label studies also recorded a high incidence of pain, burning, and stinging skin. However, the intensity of the reaction was different in that there were reports of severe pain, burning, and stinging. It was mentioned that 1 patient was hospitalized due to severe pain and treated with morphine.

So patients treated with curette-MAL-PDT could have skin ulcerations and blisters that could last 1 to 2 weeks after treatment, and in two cases erythema that lasted up to a year. Now, this was obtained from the non-U.S. labeling. The drug is marketed in Europe. Therefore, no separate analysis for these recurrences are available from the agency. And some of these came from the integrated summary of safety.

Curette-MAL-PDT was associated with a higher incidence of pain, burning, or stinging than curette. The use of anesthesia with MAL-PDT treatment was not studied in a systematic fashion. In fact, there were only 26 of the

538 patients studied who used local anesthesia. So, therefore, there's minimal instructions for the use of anesthesia, and from the proposed label insert, tumor fragments from most lesions may be removed without damaging normal skin and without the use of anesthetics.

A dermal sensitization study was performed, and these studies are generally routine with topical products that are applied. It is a study that is conducted in normal human volunteers. Sensitization was demonstrated in the dermal safety study.

There were 2 patients during the clinical trials that reported urticaria/hypersensitivity reactions, and from post-marketing there have been 2 patients with allergic reactions and 1 of them was a positive rechallenge.

I would also like to state that during the collection of adverse events during the clinical studies, the data were not collected in a fashion that we could tease out adverse events due to curetting, to the cream application, or to the illumination. So, therefore, we cannot say whether or not there were any incidents or suspicion of sensitization due to MAL cream.

The sensitization study design was as follows. There was an induction phase in which MAL and MAL vehicle were applied for 3 weeks. There was a 2-week rest period.

Then there was a challenge phase. Now, the challenge phase was a little different in that there was only a 3-hour application of MAL cream and MAL vehicle applied, and there was a 48-hour application time for the aminolevulinate .1 percent cream in soft paraffin and the vehicle for a cross-sensitization challenge.

For the dermal safety study, there were 215 planned. According to the amendment, after 156 patients were included, the other patients were not studied due to reactions suggesting sensitization in half of the first 102 patients who had been tested. Out of the 156 that were included in the study, there were 58 dropouts, and these patients may have already been sensitized. There were 98 who agreed to continue to the challenge phase.

In the challenge phase, there were 40 patients who refused to have MAL cream applied and there were 58 patients who were challenged with MAL cream. So out of the 58 who were challenged with the MAL cream, there were 30 that were considered positive. There were 3 that were considered equivocal, and there were 25 negative. So from this study in normal human volunteers at least up to 52 percent of the 58 subjects, not counting the 58 who dropped out, who continued and did not refuse to have MAL cream applied, were sensitized to MAL cream.

The ALA 48-hour cross-sensitization challenge

was tested in 98 patients. Out of this group, none were judged positive to .1 percent ALA. 2 percent were judged with equivocal reactions to ALA, and 2 percent were judged positive to soft yellow paraffin vehicle that was used for the ALA.

So in conclusion, MAL cream has an unusually high contact sensitization potential of at least a 52 percent sensitization rate in a provocative study. Cross-sensitization to ALA, an endogenous substance, cannot be ruled out by this study that was conducted. And sensitization of MAL cream of health care workers and of patients are of concern.

In summary, the curette-MAL-PDT has been shown to be statistically superior to curette-vehicle-PDT for the chosen outcome assessment in the pivotal studies, and we are asking the committee to consider the adequacy of these studies for estimating the treatment effect based on the early histology and the small number of patients studied in the pivotal studies, the minimal recurrence rate data for primary nodular BCC that was submitted.

We'd also like for you to discuss the adequacy of instructions for lesion preparation due to an apparent high vehicle-PDT response rate and a wide center-to-center variability.

A numerically higher recurrence rate with MAL

versus surgery in one small open-label study was seen. The exact point estimate is uncertain.

For safety, we would like for you to discuss pain and minimal information regarding anesthesia and pain control since anesthesia was not systematically studied and pain could range from moderate to severe, and also the unusually high contact sensitization rate seen in the study conducted.

This is an example of the CureLight lamp which is an integral part of this application.

DR. STERN: Thank you very much.

What I'd like to do is first start with questions to the agency about their presentation, and if we've concluded those specific questions, then we may have more general questions starting before lunch, if there's time, but until we've completed questions about the presentation, it should be strictly for the agency at this time.

Dr. Plott?

DR. PLOTT: Dr. Vaughan, I wonder if you would answer a question. After the agency gave the sponsor direction for an endpoint of clinical and histologic cure as their primary endpoint, they chose to go on to just look at histology. Could you explain the agency's position for choosing that combined endpoint, and why is that important?

And is that consistent with other applications of other products that are being looked at that might combine clinical and laboratory endpoints?

DR. LUKE: With regard to basal cell carcinoma, which is a tumor, a clinical response is thought to give you a preliminary survey of whether there is tumor there or not and followed by a histologic evaluation of whether, indeed, there are tumor cells present, knowing that you knew at one point there were already tumor cells from the initial biopsy. This is the rationale for obtaining both a clinical and a histological endpoint.

DR. KATZ: A question to Dr. Hansson. Dr. Hansson, the first clinical photo you showed a person with basal cell on the nose previously treated with Mohs.

DR. STERN: I'm sorry. We shouldn't go to the sponsor until we've finished the questions for the FDA.

DR. KATZ: Oh, I thought we were asking actual questions.

DR. STERN: No. I'm sorry. First, the questions for the FDA presentation, and then we'll have questions for anyone. I'm sorry.

DR. DRAKE: Dr. Vaughan, the missing data, the missing cases you rolled into potentially active tumors. I'm not sure how to ask this question, but when we were doing guidelines for the American Academy of Dermatology,

what we found is a lot of these people disappear because they're well because they don't have any more tumor. So did you also roll the data in to assume these 40 had been cured and didn't need to come back? I mean, you certainly rolled them in because you made the assumption they might not be cured. Did you look at it in the reverse manner too?

DR. VAUGHAN: Yes. Actually that's how PhotoCure approached the recurrence data. The missing patients were not included. Therefore, we have rates with the missing data, without the missing data, and per-protocol recurrence rates.

DR. STERN: Lynn, they were in the column before that very last. They were in the top of the last column, the simple proportion --

DR. DRAKE: I know what the sponsor did.

DR. STERN: No, no. In her presentation. If you could go back to that slide.

DR. DRAKE: Well, I misunderstood then because it impressed me that she had what was real and then she rolled in the missing as active lesions. And I want to know what if she rolled them in as a successfully treated lesion.

DR. STERN: She did that on the top number.

DR. VAUGHAN: It would be the recurrence. We

gave two --

DR. KATZ: 9 percent.

DR. DRAKE: So the 9 percent included? I remember the 9 percent number. You assumed that all the missing data was cured?

DR. VAUGHAN: Slide 16.

DR. DRAKE: I want her to answer it, Rob.

DR. VAUGHAN: Which slide are you referring to? Slide 32? Sorry. Slide 32, page 16, slide 32.

DR. DRAKE: I remember the slide. I know exactly the slide.

DR. VAUGHAN: The top number will give you the number of actual clinical recurrences.

DR. DRAKE: That's actual. Then you took the missing data and you assumed that they were bad.

DR. VAUGHAN: So, therefore, if it wasn't reported as recurrent, then it wasn't counted as a bad outcome.

DR. DRAKE: But it also wasn't counted as a positive outcome. In other words, if you added all those missing cases to the actual lesions, you would have an improvement in the outcome.

DR. STERN: If you look, the denominator for both the -- it's 4 over 47 people in the trial. That's the number of tumors over the number of people or lesions.

I've forgotten which.

DR. VAUGHAN: Lesions.

DR. STERN: 9 percent. That's your conservative assumption that everybody who didn't come back was cured. And the lower one is the 16 over 47 assuming everybody that didn't come back had a tumor. The denominators are the same.

DR. DRAKE: Got you. Thank you very much.

DR. STERN: To me what's interesting in looking at these data is the differential in the number of people who did not return. I think a conservative assumption is to assume that the difference in the non-returnees are the unhappy people who went elsewhere. So, for example, if you have symmetrical not follow-up, then you'd say, well, it's probably equal reasons in each or you could project the rates forward using the smaller denominators, a whole variety of ways.

But if you look at these data, what interested me is -- and I've forgotten the exact numbers. I think it was 12 versus 8 or 12 versus 7. So the question is why should a higher proportion, 12 out of 47 versus 7 out of 51, decide not to come back. I think in a lot of studies, when you're trying to do certain endpoints, you really look at that difference in failure to follow-up as a signal for why didn't they come back since it's a randomized study at

the beginning.

DR. DRAKE: Well, Rob, I understand what you're saying. I understand what you're telling me about the denominator, but to assume that people don't come back because they're unhappy is, I think, an incorrect assumption because, for starters, if you look at the cosmetic results, the patients were far happier with the cosmetic results from this treatment and from curetting than they were from surgery. So it could be they didn't come back because they were very happy with the cosmetic result whereas the surgical patients came back more because they were unhappy about the scars. So I don't think you can make that assumption. People don't come back and the fact of the matter is we have no idea why they don't come back.

DR. KATZ: Since we're discussing page 16, this slide, we really shouldn't confuse things with cosmetic and cure rate. Let's compare apples and apples. Assuming the company's data of everybody cleared up that didn't come back, you've got more than four times as many recurrences percentage-wise in the MAL group as in the surgery group. Four times as much. This is with 2-year follow-up; 9 percent recurrence at 2 years with the already intuitive data that we have with 5-year follow-up with surgery with a recurrence rate of less than 5 percent.

It's counterintuitive to assume that all those folks didn't come back in the MAL group because they were cured when we know from the early studies described that only 47 percent over placebo were cured at 6 months or 3 months or whenever that was. So to assume that these other folks, these 16 people, didn't come back because they were cured, when we already know from the previous studies that only 47 percent are cured at the 6-month follow-up, it's quite counterintuitive.

DR. STERN: I'm sorry. Dr. King.

DR. KING: I still come back to the question the agency is going to ask, I think, which is what is the potential for complications with the people who apply it, the health care workers, and how do you do prescreening to find out who may be unusually phototoxic. To put somebody in the hospital at Vanderbilt for applying light requiring morphine, et cetera, gets you a line of lawyers you won't believe. So I think that I'm looking for some direction of what the agency is looking for that we should examine for instructions.

DR. WILKIN: Well, I think there are two pieces to this. The first piece is that it's difficult in the clinical study setting, outside of a dermal sensitization study in normal subjects, to actually be thinking about the difference between phototoxicity and contact

hypersensitization. The skin has a limited repertoire in acting against noxious substances: erythema, blistering, those sorts of things. It's difficult sometimes to tease out exactly what the causal mechanism might be.

On the other hand, the provocative dermal sensitization study says that it has the potential to have sensitization. That's what we learn from those dermal kinds of studies.

The concern is for both patients who -- if someone has a basal cell, it's very likely that they're going to have a basal cell carcinoma in the future. But the staff at a treatment site would presumably have much greater exposure. I think it's interesting that the sponsor has not found this to be a problem. So we have the apparent absence of a problem in real practice, but in a provocative study which is sort of an intense, provocative way of finding out if there's any potential, it's telling us a different sort of thing. So part of our question for the committee is to try to put that together and give some feedback.

DR. STERN: Dr. Ringel.

DR. RINGEL: I'm going to try not to get lost in terminology, which I find myself doing. The recurrence rate and the failure rate. I take it that the recurrence rate only applies to people who at 3 months had a complete

response, and then you followed them for a recurrence rate. Whereas, a failure rate really is trying to say who didn't respond to this treatment at the point you're looking at them.

DR. VAUGHAN: Yes, that's how the data was assessed.

DR. RINGEL: It's odd because with surgery, if we're talking about a recurrence rate, if you look at someone 3 months post-op, you're just going to say they recurred; whereas with this study, if they didn't respond, you're not even considering those.

I guess what I'm saying is why ever are we looking at recurrence rates at all? It seems to me we should only be considering failure rates. What I want to know when I'm treating someone is they have a basal cell carcinoma at point 0, 2 years from now, what's the likelihood of their having basal cell carcinoma. And that's the failure rate, not the recurrence rate, it seems to me.

DR. VAUGHAN: Could you put up slide 33 please?

Let me understand your question again. The last part of your question again is why are we concerned about the recurrence rate 2 years later?

DR. RINGEL: Yes.

DR. VAUGHAN: Because basal cell cancers are

looked at in terms of cure, as Dr. Stern mentioned earlier today, in terms of years. 5 years is short-term. Beyond 5 years is long-term. So we want to follow that as an integral part of efficacy. Generally you treat a patient and you bring them back 6 months to a year for follow-up, but it was the design of this study to bring patients back at 3 months to assess whether additional treatment is needed.

DR. RINGEL: I understand why it's a long-term study. What I don't understand is why we need to characterize that long-term study in terms of recurrence rates which seems to leave out a part of the population which was initially treated. If you're really doing an intent-to-treat, you will take a look at the entire population which is your failure rate.

DR. VAUGHAN: Well, that's what the failure rate does.

DR. RINGEL: Yes. I think that we should be focusing on this slide rather than the recurrence rate slide. That's what I'm saying.

DR. STERN: Dr. Tan.

DR. TAN: Yes. We talk about the study has a very small sample size. I just have a simple question I'm curious about. Was the randomized trial designed with detecting a 30 percent difference and if the trial was

conducted in a way following the protocol, originally designed?

DR. ALOSH: Yes, as I mentioned we have this communication between the sponsor and the agency about the design of the trial. The study was designed to give comment about the endpoint, and the power of the study would be related, as you know, to the endpoint which you are assessing. So we gave the endpoint. The endpoint should be clinical as well as histological evaluation, but even though those comments -- they were on March 7, 2000 -- the sponsor and the protocol in August maintained to have histology. So this is why I think the efficacy result wasn't the same if you look to histology alone versus histology and the clinical evaluation which was requested by the agency.

DR. TAN: So the trial was designed to detect probably a 30 percent difference in response rate. So, therefore, the trial was designed as having 30-some patients in each arm.

DR. ALOSH: That's right. I think there is communication. Probably the sponsor could provide more detail, but I think the issue of powering the studies really are related to the endpoint, and what we feel between the sponsor and the agency, we did not have the same endpoint. We gave comment, again as I said, clinical

and histology, but we got something back in terms of histology alone.

DR. STERN: Could you just clarify your response? I had thought I saw a slide where the agency made a specific recommendation about sample size for evaluation of nodular which was different than I think I understand the number of analyzable cases that have been presented today. Could you refresh our memory? I had thought there was some number like 250 that you were asking for -- that the agency suggested, I should say, in terms of powering the study.

DR. WILKIN: Actually that was in terms of recurrence data. It wasn't with the two pivotal -- that's right. The randomized.

I think Dr. Clementi accurately, in his slide 15, documented the division/sponsor meetings where we did have a lot of communication. There was a pre-IND meeting in August of 1999, a phase II meeting in March of 2000, a pre-NDA meeting June of 2002.

I would say if you look in, again, the CFR, Code of Federal Regulations at section 312.47, it talks about meetings between FDA and sponsors. It emphasizes the need for good communications and it also mentions a pivotal meeting is the end-of-phase II meeting.

We did have, I think, in addition to what Dr.

Clementi is listing, a teleconference that did focus on some aspects of basal cell carcinoma in addition. So I think there's even one more where we got to spend some time together.

Then if you look in 312.47, it talks about if one comes to the very end at the pre-NDA meeting, normally that's a meeting where the sponsor and the agency groups meet and they talk about format and content, what should be in the NDA, how it should be organized so that our review team can very efficiently get into it and review the data. But in the regs, it also speaks to any additional aspects that haven't been closed on should be discussed at that time. I think that that was a fairly substantive meeting in terms of identifying those additional sorts of things.

I have no doubt the sponsor believes that they have addressed the spirit of what the agency has asked for. On the other hand, it's not quite the same thing as having an end-of-phase II kind of an agreement which we are able to achieve in some circumstances. So I don't want to make too much of this. I'm just saying I think they heard advice and then made some decisions as to what they thought would be compelling, and when the NDA came in, we looked at the NDA and we frankly thought that there was sufficient information to file it and review it and consider this.

DR. TEN HAVE: I have a question for Dr. Alosh

in terms of the variability of outcome for the two cycles of treatment. Correct me if I'm wrong, but it appears that most of the variability is in the outcome in the first cycle, but when you consider both the first and second cycles, there's less variability across the centers. If that is an accurate summary of what you were presenting and given all the problems with the study design looking at the first cycle and looking at outcomes in the first cycle given that some of the partial responders are then treated subsequently, can you re-explain your rationale for focusing on the first cycle in spite of those problems and given that there seem to be less problems with variability across center for the first and second cycles? Does that make sense?

DR. ALOSH: Well, I agree. This is study 307. All right. For the first cycle, really the interaction was there, and I think I stated that this wasn't the primary endpoint to have the first cycle. However, we felt data from the first cycle, it's the largest -- to include the largest number of lesions to be analyzed, because everyone is treated once. What we have, the number of lesions I think which went through the second cycle, roughly I'd say around 10. I don't have the exact number.

But I agree and I stated this. I thought the interaction is significant only for the first cycle. If

you look to the first and second cycle combined, the Breslow data still gives you a p value of .134, which is not significant. We judge it by the p value, as you know, .10. So it's close.

But I think the point here, if you look to the last two columns, the Breslow-Day test gives you .31, and this is based on histological evaluation only, which is the endpoint the sponsor analyzed. So the point here, you could see the center-by- treatment interaction, the magnitude of that, it depends on how the endpoints are evaluated. If you consider histology alone, you could see there is no significant treatment-by-center interaction, .3 compared to .1. If you consider clinical and histological, you see .13, which is close to the .1. I agree. Interaction is really for the first cycle. I want to emphasize that this is the biggest set.

DR. STERN: So let us now go on to questions to both the sponsor and the FDA with any parts of the application. Michael?

DR. BIGBY: This question is to the sponsor. Can you put up your table 37? It's section 7.2.1.5.1 in your book. It's table 37. This is with regard to studies 307 and 308.

Just sort of as a background, the reason for doing a placebo-controlled trial is to separate the

treatment effect of the active treatment versus all the nonspecific things that go on in a trial. And efficacy is usually measured based on the difference between active treatment and placebo. The disturbing thing from this table is that if you look at that column, the difference in both of the studies is either 42 or 48 percent and the confidence interval goes from 18 to 72 percent. So that really is the treatment effect, not 76 or 77 percent. The real treatment effect is the difference between placebo and MAL-PDT.

I just wanted to know the sponsor's response to a 95 percent confidence interval of the actual treatment effect being, one, that wide and also that potentially low so that could have a treatment effect of this treatment as low as 18 percent if you looked at the 95 percent confidence interval.

DR. MORRIS: I'm Hilde Morris. I'm the Director of Clinical Research at PhotoCure.

I think you have to look at the treatment as a whole. It consists not only of the cream. It consists of the preparation procedure, the application of the cream, and the illumination, and you can't really take out one of those parts of the treatment. So when we did our vehicle-controlled studies, we had all the other elements. So you can say that the part of the treatment that's attributable

to the active substance in the cream is what you are pointing out here, but in fact, the efficacy of MAL-PDT includes all of the parts of the treatment.

DR. BIGBY: I have to say that I sort of disagree with that entirely and that you're not trying to market just the light or just the curettage. You're trying to market MAL-PDT. And if you do a placebo-controlled trial, the actual treatment effect is that which is different from your control. Now, you can argue that you picked the wrong control, but you can't say that you do a placebo-controlled trial and not want to accept the difference in the treatment as the real treatment effect. I mean, that's just sort of the basic principle of doing controlled trials.

Another question. Table 42.

DR. KATZ: What page?

DR. BIGBY: Page 95.

So this was the versus surgery estimate. Just one clarification question. In the ITT analysis down at the bottom, when you look at the difference, you wrote an "N/A" under ITT. Why is that N/A? In the ITT analysis, when you look at the estimate of the difference between surgery and MAL-PDT, there's an N/A under ITT analysis, and I wondered why that's there.

DR. MORRIS: The primary analysis in this study

was the per-protocol analysis, as we discussed also with the FDA since that's the most conservative way of looking at a non-inferiority trial.

DR. BIGBY: Absolutely not. It's just the opposite. The ITT analysis is the most conservative way. So why is that an N/A?

DR. MORRIS: Not for the non-inferiority trials.

Maybe you want to say something, Per Fuglerud, our statistician.

DR. 8: Yes. I think I don't totally agree with you that the intention-to-treat is the most conservative comparison when you want to show non-inferiority because in an intention-to-treat population you include all patients and that could reduce the difference between the two treatments. And a more conservative way will be only to use the per-protocol population because that will not reduce the difference between the treatments.

DR. BIGBY: Okay. Well, is it possible for you by the end of the day to fill in that number?

DR. 8: Yes. It's 14.6.

DR. BIGBY: So it's 14.6 percent.

DR. 8: That's correct.

DR. BIGBY: Thank you.

And then the confidence interval is what?

DR. 8: Sorry?

DR. BIGBY: The confidence interval of the number is what?

DR. 8: That's the lower confidence limit. I think we also have the upper. We will bring it to you during the day.

DR. BIGBY: So this is my question, though. You say what you would have accepted was an upper 97.5 confidence interval was less than 15 percent. This is a study that has a relatively small number of patients. So what is the power of this study to actually demonstrate that difference?

DR. 8: 90 percent.

DR. BIGBY: 90?

DR. 8: Yes.

DR. STERN: Are you sure that with an alpha of .05, the beta type 2 error is .1 with a study of this size with these rates? That seems like a heck of a lot of power to exclude a 15 percent difference, but I didn't do the calculations.

DR. 8: The calculation is described in the protocol and the power is 90 percent in this calculation.

DR. STERN: With about 50 people in each arm.

DR. 8: Yes.

DR. STERN: And the expected rate in the

baseline was 5 percent in the calculation and the comparator group --

DR. 8: We expect a response of surgery of 92.5 percent, a complete response rate, and we assumed that model was the same.

DR. STERN: And you were 90 percent confident that if the real rate difference was 15 percent, you would detect that in a 50/50 study.

DR. 8: With a 90 percent power, yes.

DR. MORRIS: Can I say something about the interpretation of this study because I think we all agree that although it does end on the right side of the statistical significance here, it is borderline at this 3-month assessment time point. I think we do realize that the difference increases over time, and we have said in our conclusions that the response rate for MAL-PDT is slightly lower than surgery, at least when you look over time. However, we believe that in a risk-benefit assessment, that there are other aspects of the treatment that can make it a useful tool in some patients.

DR. BIGBY: I've got a couple more. Page 110. This is a procedural question. The description of cryotherapy is rather brief, and it basically said it was done for a minimum of 20 seconds and there were two cycles. Do you have the data about what was the range and median

and maximum for cryotherapy and it how it was determined how long to freeze a lesion?

DR. 8: Can you please repeat the question?

DR. BIGBY: The only thing that you said about cryotherapy was that it was a minimum of 20 seconds. Now, having treated many basal cells with cryotherapy, I've never treated anybody with as little as 20 seconds. So what I want to know is what was the range of cryotherapeutic treatments, the median and the maximum, and how was it determined how long to freeze things.

My skeptical reaction to this study is that what you've shown in this study is that MAL-PDT is more effective than sort of inadequate cryotherapy.

DR. STERN: And I guess the other question is if the cryotherapy were adequate, how can these recurrence or failure rates be so much higher than any of the published data for the type of lesions that you've treated not for canthal lesions or very severe sites, but of the type of lesions you've treated, the whole literature would suggest a fraction of this recurrence rate. So in fact there's consistency between what at least Michael and I learned as the adequate treatment with cryosurgery, what we would consider inadequate by our clinical standards at a higher recurrence rate than published in the literature.

DR. MORRIS: On our side, 67 in the

presentation today, we had the specification of the cryotherapy. They were supposed to freeze until they obtained a rim zone of 3 millimeters around the lesion and then to thaw, and the thaw time was to be two to three times the freeze time, and then a repeat freeze session. So that was how that was described.

I think that when you look at our data compared to what is in the literature, our data is prospective and randomized data, and in the literature, I think you only find studies that are retrospective, and they will invariably have different response rates than a well-designed, controlled study.

We've seen that in our AK studies too where we also compared to cryotherapy, and again, cryotherapy had also in those studies much lower response rates than the retrospective studies in the literature would indicate. There are no studies that have prospectively compared cryotherapy to other treatments in AK and multi-center.

DR. BIGBY: Okay, but do you have recorded what the range, median and maximum, was for cryotherapy?

DR. MORRIS: Yes, we do have those numbers, but I'd have to go find them for you and I can get them during the day today.

DR. BIGBY: I have just two more. With this question of sensitization, have the patients who had

standard MAL-PDT treatment, two sessions and then another two sessions 3 months later if they had partial response, been patch-tested to see if they are sensitized to MAL?

DR. MORRIS: No, they have not been.

DR. BIGBY: So you don't actually know if in normal use the patients get sensitized to MAL.

DR. MORRIS: No. Maybe you want to talk about these cases.

DR. POSNER: You're correct. We do not know what the incidence of contact sensitization is. What one can say, however, is that it hasn't been a clinical problem. Perhaps a suspected case has not been a difficult problem to manage and certainly investigators haven't found this as an issue. We are talking, of course, about contact dermatitis and nothing worse.

DR. STERN: I don't know how you would tell that. The only time that these people are exposed are at the time they're also getting light, which would give them an erythema and blistering reaction that at least I would challenge anyone to tell whether there was also a contact dermatitis going on. The only way you could test for sensitization in any clinically meaningful way would be a subsequent rechallenge on a distant site away from the treated area.

So the fact that no one reported it -- sure,

it's hard to tell a contact reaction after someone has had a severe phototoxic reaction in the site. I just don't think you could tell which was which and one would reasonably suspect that it was a phototoxic reaction which is part of the therapy and you couldn't separate them.

DR. PARISER: Let me just say that in routine use of this in the trials, the use of the modality in the trials, I think you possibly could tell under an occlusive patch test, if you will, considering the application to be an occlusive test. The patients routinely and regularly had these burning and skin sensitization -- not sensitization -- skin burning, crusting, a little oozing. That was normal. A rip-roaring contact dermatitis under a patch for 3 hours could have, not always, made some kind of difference. There didn't seem to be a subgroup of patients where that happened.

DR. STERN: I live in an area surrounded by poison ivy, and a far smaller proportion of poison ivy reactions display what's described for oozing, crusting, and blistering with the phototoxic reactions. So again, perhaps you could detect them, but I would be clinically challenged in being able to differentiate those in the clinical setting of this therapy. It don't make sense to me.

DR. PARISER: I'm not saying you can. But what

if you put poison ivy under a patch for 3 hours? It does make a difference I think.

DR. LUKE: Just to be helpful, we're looking at page 157 of the sponsor's briefing packet. There are two cases that you're discussing, the two so-called eczemas. One patient had eczema on the face and the other patient had acute eczema. Both of those were thought to be possibly suggestive of relationship to the product. In one case there was a hypersensitivity test performed by an astute dermatologist which reviewed sensitivity to both ALA, the endogenous substance, and MAL cream.

DR. BIGBY: This is my last one. Page 125.

DR. POSNER: Sorry. Could I just clarify one issue there? The patient had also been treated with ALA at a different site and was positive when initially tested, but when they came back 6 weeks later, the response was really negative except a very weak response to a very high concentration of ALA, but undoubtedly a positive reaction to MAL. So that is the one confirmed case that, as you say, the astute physician did test with patch test.

DR. BIGBY: This is my last one. Page 125, the patient that's shown there. When was he treated and what's his current status?

DR. MURRELL: This patient was from Dr. Vinciullo's center in Perth, and my understanding from the

sponsor and the data is that at 2 years follow-up, which is the latest data that we have in the Australian high-risk study, is that the patient is clinically negative. But we're not doing biopsies at the 1-year follow-up because otherwise, there would be no tumor left to keep on assessing by 5 years.

DR. DRAKE: Can I follow up on what she just said? Why would you want tumor left to keep on assessing in 5 years? She just said there would be no tumor left to keep on assessing. Why would you want tumor left?

DR. MURRELL: We don't want tumor left. What I meant was if we had done biopsies on every single time we assessed the patient, you might have an argument to say there was no recurrence because you had physically removed it all.

DR. KING: Really probing the question of how do you know about localization, in slide 6 it says there's minimum systemic uptake due to low ability to cross the basal membrane. I don't believe that for a minute, given the size of the porphyrin.

So I come back to you found that 160 milligrams per kilogram led to a plateau. Is that possible like griseofulvin and other molecules the epidermis is acting as a sponge? You're really just soaking up the MAL and the fact it doesn't get through is more related you don't put

on too much, so you're not going to get much through.

You really didn't challenge the barrier in the usual sense. You're just putting on MAL and saying what the absorption is into the epidermis. To say it doesn't get through to the dermis or to the blood vessels seems unbelievable to me.

DR. HANSSON: I agree. It sounded unbelievable to me as well. However, if you look somewhere in this briefing document, the first observation that really caused interest in this issue for us, before we did the transepidermal in a cadaver for a type of skin test for objective measurements, for some reason we found very, very low uptake of MAL compared to ALA and to what other people have reported for ALA.

If you look at page 19 in the briefing document, the nude mouse is a good friend of us because due to a very thin stratum corneum, they have a fairly rapid exfoliation of the superficial cells and a similar high proliferation of the basal cells to replace what is falling off.

We have been using the skin of the nude mice to test porphyrin buildup and doing a lot of kinetic studies both with porphyrin formation and porphyrin removal. One of the things we really discovered in the mid-'90s or early '90s was that when we used aminolevulinic acid derivatives

where we have blocked the carboxy part of the molecule, the buildup of fluorescence always only came at the site of location. If we put the free carboxylic acid -- you have the picture to the left -- you get some local buildup in the beginning, but very soon the whole mouse became red.

If you go into our preclinical package -- I'm too old to have a very good memory, but I think the uptake in the skin patch test was something like .06 microgram per square centimeter and a depot of approximately 3, 4, 5 percent of the total dose applied. It was a very high dose and the systemic uptake from 4 grams -- was that correct -- was approximately 100 micrograms calculated.

If we did exactly the same thing for the free carboxylic acid -- or it actually has been reviewed by the agency for another product for actinic keratosis in this country. They have exactly the same test providing figures which are 10 to 20 times higher that we get in exactly the same studies.

So you say you would never have believed it, and I agree with you completely. I would never have believed it. If you ask me for an explanation, I would just say I really cannot provide it.

DR. KING: I still don't believe your explanation. It looks like a thumbprint. Having worked with mice for about 15 years now, I know they have a

thicker skin or epidermis than the normal furred mouse. So when you look at what you're looking at, you almost look like if you took poison ivy and put it on there, in fact stopped. If it was stopped by the basal membrane, it would be spreading out this way as opposed to straight down type thing.

So I don't want to quibble a point, but I know you're saying it doesn't penetrate very well, and I was suggesting that's what happening is it's being selectively absorbed by keratin, something in the cytosol or mitochondria only at that site. So that's why you get a limitation. You're implying a barrier this way, but you don't explain why it doesn't spread out this way.

So I like the poison ivy analogy, so I just wondered if you had an explanation. Maybe if you did a subset or fractionization, you could find out whether it's not only in the mitochondria but in the cytosol, keratin, or other kinds of things different from ALA. Is that making sense there?

You put a thumbprint. You get the chemical right there. Poison ivy. If you put this on here and it doesn't go through like this, that's different from saying you got stopped by the relatively permeable basement membrane. That means it must have stuck to the type 4 collagen, et cetera, et cetera. So you're now off into

basic science, so I stop right there.

DR. HANSSON: I probably agree with you except I didn't understand everything you said. Perhaps the formulation that it doesn't seem to penetrate the basal membrane may not be a good one. But when we do all systemic measurements in all the organs, when you apply the free carboxylic acid, after 8 or 12 or 24 hours most of it ends up in the liver. If you do that with the derivatives, with a single carbon or a 6-carbon, nothing ends up in the liver. Honestly, I don't know the explanation.

DR. KING: Sure, great.

DR. TEN HAVE: I have two questions clarifying some points that Dr. Bigby raised for Dr. Alosh. One is a more general question about what the FDA allows in the U.S. in terms of the primary analysis, whether it's an intent-to-treat analysis or a per-protocol analysis.

The second question, I think which is more pertinent to this particular presentation, is what is the threshold for inferiority deficits or treatment deficits. The sponsor appears to be using 15 percent as a clinically tolerable inferiority deficit in terms of 15 percentage points. What does the FDA accept as a clinically tolerable inferiority deficit?

DR. ALOSH: Thank you. I think, Dr. Ten Have, probably you are touching on the non-inferiority trials,

the European trials. In terms of those trials, really the agency did not have input in terms of the protocol. Those trials were completed before the sponsor came to the agency. So we did not have much to say in terms of the non-inferiority margin.

I'll answer the two points which Dr. Ten Have phrased in sequence.

First, in terms of analysis, we used the ITT as well as the per-protocol analysis. The statement that for non-inferiority trials we used the per-protocol, it's conservative, myself, I do not agree with that statement. I think the ICH-9 talked about a superiority trial to use the ITT. It left it open in terms of the non-inferiority trials.

If you look to the European guidance, it talks about both of them, to have the ITT as well as the per-protocol.

Lately in 2003, there is a paper in Statin Medicine which talks also about having the two analyses. Consistently we have been asking for the two analyses, the ITT and the per-protocol population.

The way I see it's conservative, only in terms of reduction in the number of patients. Consequently you will end up with larger confidence intervals. But what are the characteristics of those patients who are dropouts from

the ITT to reach to the per-protocol?

So this is really left to have been consistent in asking for the two populations, for the ITT as well as the per-protocol, retrospective as I said. We weren't consulted. The sponsor did not submit the protocol to the agency for comments for those.

Concerning the second part about using a non-inferiority margin of 15 percent, it's really a clinical stat issue. In a way what's the margin which you might think clinically could you do with that. But I'd say the stat part at least -- I mean, I leave it to clinicians to answer whether the 15 percent is relevant or not. I'm sorry. Do you want to answer or should I just continue and then you could answer?

DR. MORRIS: I can just clarify how we reached the 15 percent. It was agreed upon by the dermatologists who were the investigators in the trial and it was a consensus among these dermatologists that 15 percent was a difference that they would say was clinically relevant.

DR. ALOSH: That's fine. It's true you might agree with the dermatologists, but I'm stating what we do in the agency.

We have in the past some guidance. For the higher response rate, we'll use a small non-inferiority margin. In particular, the response rate of 95 percent

entire, we use 5 percent. If it is 90 percent entire, we used to use 10 percent. Now, I'll go back. They were a few years ago and we are not enforcing them now. But the message I think, the higher the response rate, we'd expect a smaller non-inferiority margin. And it's also to discuss with the clinical to see how important it is.

There is another issue in open-label studies which is really gaining momentum. There is no vehicle arm in those open-label studies, and consequently, for the validity of those studies to be established, you need to have the vehicle arm in those studies.

So from a statistical analysis point of view, I think we have several concerns, I mean, about submitting was the patient population which Dr. Ten Have tried to touch like the analysis for two populations. I think the more serious is the non-inferiority margin. There is no vehicle arm. So I don't know if I addressed your question. Thank you.

DR. STERN: I would suggest that after lunch the panel directly address the issue of what difference in outcomes between accepted therapy and the sponsor's therapy would be considered to be clinically meaningful. In other words, do we agree that a 15 percent inferiority at the time of measurement at 1 and 2 years is clinically, in fact, acceptable for a therapy. I would suggest we just

put that in our computers and not get to it until after lunch because I think one of the things the agency might want is our opinion about what's a meaningful difference in outcomes as opposed to what the investigators might have said. So let's not discuss it now but put it down on our agenda.

I think we have very quickly three more people to ask quick questions, and we can always ask longer ones after lunch. Jimmy?

DR. SCHMIDT: I'd like to ask a question to Professor Murrell. On page 107, in the study 304, you treated extremities. One of the banes of my existence is these people who are coming in now with these superficial basal cells on their lower extremities and also transplant patients. Can you elaborate on what your results were with those patients? Were you successful with the basal cells on the lower extremities? Because there's no rate of whether they recurred or what happened.

DR. MURRELL: The 304 study wasn't one of the studies that I presented. I presented the 310 and the 205, which were the uncontrolled studies. Per, our statistician, is looking up to see what the subgroup analysis for that particular location was because I don't know is the honest answer.

But from the point of the view of the patients

that I personally treated with that, they did complete response. So they did well, but that's just a small group of my own personal experience with those patients. So we'll have to tell you later if you want specific numbers.

DR. SCHMIDT: Thank you.

DR. RINGEL: I had a bunch of questions, but I'm just going to limit it to one.

DR. STERN: Perhaps, if you have a bunch, maybe we should start with you after lunch. Would that be acceptable to you?

DR. RINGEL: I could do one quickly now and then do the rest after lunch.

DR. STERN: Whichever.

DR. RINGEL: The kind of burning question I had, as I was reading this, is I was imagining myself in front of the patient with a curette in my hand and they say, curette it a little bit. And I'll tell you, I just want to keep going. I really do. I just want to get rid of that sucker right there.

(Laughter.)

DR. RINGEL: I guess the question is you've compared it to surgery and you've compared it to cryosurgery. Why ever didn't you compare it to electrodesiccation and curettage? It seems to me that if I had a chance to electrodesiccate and curette a lesion twice

and then have the patient come back in 3 months and do it another two times, I think my cure rate might have been pretty good. So I guess why didn't you use that as a comparator?

DR. PARISER: Well, I really can't answer the question why didn't we use it as a comparator.

But this is not therapeutic curettage that we're all used to in curetting with the intent of cure. This is really debulking. It's surface preparation. It in general requires no local anesthesia. It sometimes doesn't even elicit much of any bleeding. So it's not therapeutic curettage. The main reason why you don't want to keep going is the patient is going to yell at you because he's not anesthetized.

Sure, a trial could be done and should be done of this procedure versus curette and electrodesiccation, but that was not in the package.

DR. STERN: If it's okay, we'll break for lunch and continue with Dr. Ringel and then Dr. Katz after lunch. We'll start back promptly at 1:00.

(Whereupon, at 12:10 p.m., the committee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:02 p.m.)

DR. STERN: I'd like to have everyone who would like to participate please take a seat, and we will start opening the meeting for the open public hearing. We have received no names at this point for anyone who would like to present at the open public hearing. So this represents, as they say in some places late at night, the final call or last call for people who would like to participate and present in the open public hearing.

(No response.)

DR. STERN: Going once. Going twice. The open public hearing is now over.

(Laughter.)

DR. STERN: Now we will continue to Dr. Steven Rotter who has been kind enough to join us from Falls Church, Virginia where he is a dermatologist in private practice and he will tell us more about his background and training and talk to us about cold steel and Mohs micrographic surgery and their efficacy in nodular basal cell carcinoma.

DR. ROTTER: Hello. Thanks for having me. My name is Steve Rotter. I do skin surgery only in my practice. I specialize mostly in Mohs micrographic surgery, but basically all skin surgery from laser down.

So I have experience with most of the treatment modalities for skin cancer, although certainly not all.

I was asked to talk about Mohs micrographic surgery. I have a canned lecture. I found out recently it should be a little bit different. So I put some slides together that I'll show you and then I'll be available for any questions that you have.

My training, if you want to know, is I was a resident with Kathy O'Connell at Hopkins and then I did a derm surgery fellowship at the University of Pennsylvania. Before that, I did two years of general surgery at Sinai Hospital, so I saw all kinds of ways to treat skin lesions. The bias of my practice obviously is Mohs micrographic surgery.

I'm going to fly through this very quickly because we only have a few minutes. I'm going to extremely quickly, and then I'm going to stop at a few points. Even after the end, there are some slides that I added in here that you'll like and I have taken out some. I'm going to explain to you what Mohs micrographic surgery is. I'm going to explain to you about skin cancer.

Obviously, we all know there's a zillion cases of skin cancer in this country. It's epidemic. 54,000-plus is the new estimate for melanoma.

We know why there's an increase. We're not

exactly sure, but increased sun habits and ozone. Obviously, history of radiation exposure, tanning beds, ultraviolet light, et cetera, chemicals, farmers and people who have exposures also get increased risk of skin cancer, also family history.

Immunosuppression, chronic ulcers, virus, inherited diseases that make you more susceptible, zero dermal pigmentosa, basal cell nevus syndrome, et cetera.

Stop me if you have any questions at any time. I'm just trying to get to the main points for this which I think is comparing treatment modalities of basal cell cancer.

We're talking about basal cells. That's the most common cancer. We see 1,500-plus of those a year in my practice. The most common location unfortunately is the head and neck, unfortunately because it's a cosmetic disfigurement more than life-threatening most of the time. Thank goodness. And people that get them will get another one. So they always say, I love you but I hope I never have to see you again, and I say, well, chances are you'll be seeing me again so don't get disappointed. And that's the problem with skin cancer: once you start in that cycle of getting skin cancer, you tend to get more.

Different types of skin cancer, basal cell. This is important. I know we're focusing I think on

nodular basal cells, and I'm going to go into this later, but there are different subtypes of basal cells. They behave differently. They look differently. I could see 10 to 15 basal cells in a day and 10 to 15 of them look different from each other. So there are clinically different appearances under the microscope and I'm going to show you some of those towards the end.

The most common is the nodular basal cell, and that's the easiest to treat.

This is just an example of a pearly telangiectatic plaque, a common location. They can be pigmented. It means nothing.

Superficial or multicentric basal cell carcinomas are these kind of scaly red plaques that people get more often on the body than on the face as opposed to the other types of basal cell, but tend to be very subtle in their extension subclinically. Because they're superficial, the epidermis doesn't show much change until it gets big enough to make a change and you don't see the clinical extensions a lot of times.

Morpheaform. It's hard to see in this light perhaps, but it looks like a scar. It looks like white plaque. So here we have four different basal cells already that look different, and many more can look much different than that.

Usually it's a slow course. People say, how long do you think I've had it? It's big guesswork. I've seen basal cells that go very quickly and a lot that have been there for 10 years or treated 8 years ago and are still there and they show up with a recurrence.

They can get huge.

Under the microscope, I mentioned before, they have different pathologic characteristics, but the common characteristics are they stain a dark purple. They're peripheral palisading, which means that the cells at the edges are lined up in a row, kind of, and there's retraction. There's space between the outer layer of the cells and the surrounding stroma or the dermis or the fat or it whatever happens to be.

The last picture was not just meant for shock value but it's meant to show you that we talk lightly of basal cell carcinoma, but you really wouldn't want one. You don't want it on your face and they can get bad. And if you leave them alone, they can be destructive. We call then rodent ulcers. They never stop chewing. They're a cancer. They just chew away, so you want to get rid of them. Sometimes you get unlucky and sometimes they follow nerves or they go into bone or other things.

This brings us to the tip of the iceberg theory where what you see is not always what you get, and that is

the basis for all treatment modalities. So my standard line is, how do you know how much to treat? A doctor is going to tell you, here's what I see. I better take some normal-looking tissue around it to make sure I get it all. That statement means the following.

Typically there are extensions of the basal cell cancer into skin that still looks normal, and I'm either going to cut it out or x-ray it or scrape it or do whatever to it with some normal skin around it because I don't know where that normal skin starts and where the abnormal skins ends or anything. So I better take some extra with me. If there were no extensions, it would be very simple. We'd just take what we could see and that would be all you'd have to do, but we know that's not true. So we take extra skin.

How much? No one knows. It depends on the location. You don't want to take too much. You don't want to take not enough or you can error and take too much on one side of it and not enough on the other side of it. So you have all the different combinations.

Then we typically send it to a lab and the lab will look at a small fraction of the edges, and we'll go into that. So again, guesswork.

And because of the guesswork, you have recurrence rates. There are a million basal cells a year.

We have lots of numbers on recurrence rates. So not all studies are good and there are a lot of bad studies, but we do have lots of numbers. In a clinical practice, I can tell you the numbers are pretty accurate for what you see in practice.

We can skip this. You can scrape and burn something. That relies on the characteristic that basal cells that are nodular tend to be softer and easily scraped away from the skin if they've never been treated before. It's quick and easy. And that's just a clinical example.

Freezing is another well-known therapy.

Again, how far, how wide, et cetera are all the unknowns.

Radiation therapy we know about. I'm personally against radiation therapy for most cancers because I see what happens to people who have radiation and you get long-term changes in your skin that end up causing cancer, and whenever the radiation people tell you it's better, I still haven't seen it to be better yet. So I think of it as the last effort for certain tumors that can't be cleared for whatever reason and late in the life of somebody because it's going to cause problems later in their life.

Again, that's chronic radiation treatment now with a cancer in the middle of the radiation that's already

been radiated, and now it's a more aggressive type of tumor. So in the center of that radiation-changed skin is a more aggressive skin cancer, and he has skin that doesn't heal as well.

Again, where's your portal? How much do you radiate?

Lasers can be used for skin cancer, and I believe we're talking about photodynamic therapy some. You can use laser for photodynamic therapy or -- you may have heard this -- you can use non-laser light sources for photodynamic therapy. I don't believe there's a big difference in cure rates between the two. So non-laser light sources may be easier financially, but the clearance rates in the studies that I'm aware of run about 75 percent in the studies on the ones they've chosen to treat, which is not as good as what we can do. That may be different.

But also a point to note on this is that clinical recurrence needs to be addressed with histologic recurrence. In at least one study I'm aware of, 11 percent of the patients or 13 percent of the patients were clear clinically -- excuse me. 11 percent had recurrence clinically, but 25 percent had recurrence when they looked at it histologically. So you've got to evaluate studies clinically and histologically. That's one point that I will make.

Surgical excision. Again, we can say, well, let's guess. We'll just take a bunch of skin, 2 to 5 or 3 millimeters, or whatever we're going to do. Now, on the body you may take a little more and get away with it. That's great. Quick and easy. 15 minutes they're home and that's usually fine.

On the face you may not have 5 millimeters to take or you may not know which direction to take 5 millimeters if it's on the end of your nose or whatever. So then you have to make judgment calls, do I skimp here, do I take more there, or whatever. Every time you take a millimeter one way or the other, you're changing the wound. You're changing the characteristic of the healing. You're changing what kind of repair you need to do or not do. So, again, guesswork. But you can get good cure rates with standard surgery.

I do this, Mohs micrographic surgery. The more I do it, the more I believe in it, and the reason is you never know what you're going to get. That's why there's this tip of this iceberg theory. Mohs micrographic surgery, named after Dr. Fred Mohs, uses a microscope to generate a map to tell where the skin cancer cells extend to. So instead of guessing at margins, I'll typically take a millimeter or 2 beyond what I see, usually the thickness of my pen that I mark the circle with, cut that out.

Instead of sending that to a lab, the patient goes to the waiting room. We take the specimen in the office and we examine it and process it in a unique way, which I'll show you, which looks at 100 percent of the edges of the surgical specimen all the way around and underneath. If there is any tumor at the edge, we'll be able to see it and I can tell exactly or pretty well exactly where that tumor is, whether I need to go deeper or not, et cetera. I mark that on a map. I bring the patient back in the room, and then we go back to where we need to. I don't know how much to take, so I just take a little bit, usually, depending on the area, 1 to 2 millimeters, maybe more if there's plenty of skin there. Then I do a little bit only where we need to, and then they get a band aid and go back out to the waiting room. It takes another 35 minutes, and then we check that. If I see anything at the edges of that piece, that means I haven't quite gotten around it yet. So if there's a little extension and I've chopped part of it and I haven't got around it, I'll just keep going until I get around it.

Skin cancers are continuous in their growth pattern. They may extend out like amoebas, and cancers are like the rest of us. They tend to choose the paths of least resistance. So they'll latch onto a blood vessel or a septia in the fat or a nerve and travel along a plane

that's easy to get to. But then tend to be contiguous. They tend to be one solid mass in different shapes.

Historically Mohs surgery was mostly delegated to recurrent tumors and tumors that were large or had a high likelihood of recurrence with standard excisions. I said we have lots of numbers. We'll go into some of those. But Mohs surgery is now used for most skin cancers on the face, it seems like, where you want to preserve tissue. You don't want to take too much. So we don't take any more than we need to. We don't want to take too little and have it continue to grow. You don't want to do a flap or graft over top of what you've just cut out and hide something from recurring, but flaps and grafts necessarily look better on the face where you're moving tissue around to fix something up. So you'd like it to be clear before you move tissue around to fix up the wound from a skin cancer.

In all the studies, you'll see there's nothing that is as good as Mohs micrographic surgery, and the studies will range from about 94 to 99.something percent. The reason is, again, we take the guesswork out of the surgery. We do have errors. We do make mistakes. The processing could be wrong. The doctor has to make judgment calls sometimes. Is this a hair follicle, is this a nerve, is this a muscle sheath, is this whatever? And is this fascia or is this a tumor?

Treatments before will cause scar tissue. Scar tissue causes breaks in that contiguous mass. So now you have to try to get all the scar tissue out, or else you may miss little pockets of tumor that are no longer contiguous that are growing in separate areas.

So it's not 100 percent, but I can tell you it's 99 percent. In my practice, it's at least 99 percent. That's all anecdotal, but if you do 10,000 cases, you'll see how many recurrences you get a year, and you'll get an idea, and it's very rare if we get a recurrence.

So it's become a kind of standard of care where the tumor is in a critical location, eyelids, lips, ears, and nose; the tumor is recurrent, it's been treated before; and the tumor has ill-defined margins. So you wouldn't even know where to start your guesswork of where to cut out.

Not all basal cells are created equal. I'll show you some slides. Under the microscope, basal cell cancers have different morphologies, just like they do on the surface of the skin, and they have different behavioral characteristics. Some tend to spread out more subtly. Some tend to spread out deeper. Some are more aggressive than others. So a soft nodular basal cell would be your least aggressive and then they go up from there.

If I'm going too fast, slow me down. I want to

have time for questions.

You can do lots of tumors. We did a dermatofibrosarcoma protuberans today. That was already treated twice with standard excision.

Now, these are some numbers and I have some more for you. If you do a standard excision for nodular basal cells, you can get 90 or 92 percent recurrence. Most of the studies with Mohs are the mostly high-risk ones which you know are high recurrence, and we're still getting 96 to 99 percent. In other words, we know that the ones on the nose, eyelid, lips, and ears tend to recur more often. We know that ones that have been treated before tend to recur more often, et cetera.

This is just an example of breadloafing in a pathology lab, how you can miss tumor. If you slice one and you go and slice two and slice three and put them on a slide, you'll miss that in section B. There was a tumor extension to the margin. If you examine 100 percent of the edges, you won't miss that.

The patient on the left is the clinical lesion. The picture on the right is the extent of the actual skin cancer. So again, you can't guess, and it just comes up every day, day after day.

This is Mohs surgery. There is a study by Dr. Zitelli, a Mohs surgeon who compared costs of Mohs

micrographic, and it's a cost effective method. If you just freeze it or burn it or scrape it, it's cheaper in the short term. It may not be cheaper in the long term, but there you can get an idea of what things cost.

This is how the tissue works. You see the tumor. You scrape away the visible part. You cut out the visible part and a millimeter or 2 around it. You make hash marks so you can identify location. You cut that out. It's then mapped. That picture is what you cut out, so there's the picture of the specimen on the patient, just for diagrammatic purposes. There is the map you've made corresponding to the tissue. You mark the edges with inks.

DR. STERN: Excuse me. In the interest of time, could you concentrate in the next 5 minutes on issues related to the treatment of nodular basal cell carcinoma as a primary nonrecurrent tumor and not in terms of technique or particular procedures? We're really talking about how to treat nodular basal cells that are primary and not recurrent.

DR. ROTTER: Well, these are primary lesions, by the way.

This is what I was saying. If you're going to repair someone, you better make sure they're clear.

Now, this study looked at all studies for a 40-year period of skin cancer. There are very few studies

that give long-term follow-up, more than 2 years, more than 3 years. But surgical excision alone, 5,500 patients, the ones they chose to treat, had a 2.8 percent recurrence rate. Curettage and electrodesiccation, the numbers are a little strange, you'll see later. But they are 4.7 percent; irradiation 5.3; cryotherapy, 3.7; and Mohs, 1.4. So that's primary basal cells. That means they've never been treated before. There are all different comers, but if you lump them all together -- in other words, some are on the face, some are on the body, some are on the ear.

Primary tumors. And now you look at greater than 5-year recurrence rates, the studies that are there, 10 percent for surgical excision; 7 percent for curettage and electrodesiccation; radiation, 8.7; cryotherapy, 7.5; Mohs surgery, 1 percent. So these are more true numbers and you'll see that recurrences happen about two-thirds of the time in the first 2 or 3 years, but 20 percent of the time they recur after 5 years.

This is just showing you at 5 years, 20 percent more recurrences by definition than after 3 years. And then the same thing. It continues to go the longer you go out, so you want to look at things that have long-term.

This was a nodular basal cell. It can go deep. You'll see that's in the fat around a blood vessel, on a hair follicle.

Mixed types. You'll do a biopsy on the top. You'll end up with squamous cell and basal cell mixed on the bottom.

Infiltrative basal cell.

Mixed. On the left, you can biopsy that. On part of the lesion, you'll see a nodular basal cell on the right. You get a sclerosing basal cell. So there are lots of variables. You don't know what you're going to get to.

It's hard to compare one or the other. But about 10 percent for straight surgery, about 1 percent or so for Mohs surgery for primary lesions.

DR. STERN: Are there any questions for the speaker with respect to the outcomes and treatments of nodular primary basal cell carcinoma?

DR. DRAKE: Could we go back to that 5-year slide?

DR. ROTTER: 2.8 percent I think was the number for surgery excision, about 5 to 7 for other things.

DR. STERN: From the sponsor, yes.

DR. BRAATHEN: Lasse Braathen. I'm from Bern, originally a Norwegian. But I am the chair at the university department in Bern.

My question is, are these multi-center studies or single-center?

DR. ROTTER: This is a cumulative of 40 years

of studies that were presented that had treatment modalities, one or the other. It's 40 years of surgical excision studies, 40 years of C&E studies, 40 years of radiation studies, and then ones that had follow-up of at least 2 years were included.

DR. BRAATHEN: Retrospective compiled for many studies.

DR. ROTTER: Retrospective compiled, correct.

DR. STERN: Dr. Ten Have.

DR. TEN HAVE: Just a quick question on the next slide. I'm just curious about why the denominator for Mohs is so much smaller for less than 5 years and more than the next slide where it's 5,000.

DR. ROTTER: Right. These are long-term studies, so studies that had patients in them for under 5 years were the 367 patients that had Mohs. Follow-up for over 5 years, there were 5,600, whatever it was.

DR. TEN HAVE: So there have been a lot more long-term studies on Mohs than short-term studies.

DR. ROTTER: Correct.

DR. WILKIN: I would just point out that in FDA's briefing document that went out in advance to the committee, there is a study. I think it's the very last section. It's titled Long-term Recurrence Rates in Previously Untreated Primary Basal Cell Carcinoma:

Implications for Patient Follow-up. The first author is Dan Rowe. I think that's the source of the data, and it describes the methods.

DR. ROTTER: Yes, that's the source. Correct.

DR. STERN: And I think earlier in the morning I sort of updated that with Jean Lee's review of a subsequent review. I think all of these data are reasonably consistent with many of the caveats we've talked about.

I'd like to thank you very much for your presentation. Okay, one last question from the sponsor.

DR. CLEMENTI: My name is William Clementi.

Could you speak to the issue of restorative surgery that may be required after you perform your procedure?

DR. STERN: We're not here to compare costs in this way, and I just don't want to get into this debate, you know, is Mohs worthwhile, do you have bigger defects, should you go to the plastic surgeon. I think that is an extreme off-the-track that we could be here for 3 days about. What we're talking about is data that is directly related to basically judging and putting into perspective the efficacy of the sponsor's drug plus device and putting it in a historical context. So I just think we're going to get into a long discussion that really won't move us

forward.

DR. CLEMENTI: I don't think I used the word "cost." I think I was getting at --

DR. STERN: No, no. I said I don't want to go there.

DR. CLEMENTI: I'm not going there.

DR. ROTTER: Do you want me to answer? Okay. I'll make a comment on reconstruction after Mohs surgery. Basically you have the choices of anything. If they're small enough and we don't take much, if it's a small lesion, you can keep it small. Sometimes you can let it heal on its own. If it's more than that, then you have to repair it side to side, in a sense. If you can't repair it side to side, then you have to borrow tissue which is either a flap. If you can't repair it with a flap, then you do a graft and you move tissue from one location totally separate and put it on. All that is done the same day, and you don't know until you get there what you're going to do to the patient, but it's all part of the procedure.

Thank you very much.

DR. STERN: Just for clarification, you do let some things heal by secondary intention.

DR. ROTTER: That was the first thing. If it's small enough, we let it heal with second intention. If

not, we go to the primary closure and move along.

DR. STERN: Does the company want the 10 minutes now to, I guess, respond to some questions or make some additional statements?

DR. CLEMENTI: William Clementi again. Thanks for having the 10 minutes.

We think it's important to clarify a few points that were made this morning with respect to meeting minutes that were exchanged between the division and us and with respect to some of the methods that were used with cryotherapy and a few other computational methods that we had performed that you didn't get a chance to see. So I hope we clarify a few misunderstandings.

DR. HESTDAL: Just to go back to my last slide this morning, what we are doing is to think that the treatment with MAL-PDT is for the indication of nodular and superficial BCC where surgery is not desirable. In regard to that, I think like Dr. Wilkin said, there may have been some misunderstandings in the interpretation of the different minutes. Maybe we could have the next slide please.

In regard to the endpoints of 307 and 308, the difference between having clinical evaluation with histological verification or it was going to be dependent on both clinical and histological, this was the FDA minutes

that we received on the protocol in regard to discussion of the protocol. It says -- I am stating from the minutes -- it's clinical evaluation with histological verification at an appropriate time after last treatment. And we made the interpretation that you did a clinical evaluation at the time, and then if it was incomplete, you excised and then you verified your clinical response.

The next part is in regard to the number of patients for recurrence studies. At the meeting in June 2000, a request for follow-up data on 250 BCC patients. In the minutes, there is actually no specification that those were only nodular BCC lesions that was given. So what we have here is that we have focused on the number of high-risk and low-risk BCC patients that we had for follow-up. And in regard to high-risk -- we have 112 patients in the low-risk group, and 196 patients, and that adds up 308 patients in total for recurrence for 2 years follow-up. So I just want to clarify that.

It's maybe also just a small point in regard to the biostatistics person in regard to ITT and PP. The 303 protocol and the 304 protocol were submitted to the agency, and we got feedback from the agency on that protocol. For efficacy analysis, the division recommended using the ITT population to establish superiority and per-protocol population to establish non-inferiority.

DR. STERN: Could we go back to your first slide? I guess I'm very confused here because most of the data that you've presented, or a large proportion of it, are in fact people who ended up having surgical excisions. So how did you get through an ethics committee when you're trying to treat lesions that surgery is not desirable and yet part of the protocol is ultimately taking the treated area and surgically excising it?

We always want the data to come from the population for which the indication is looked for. If that were the indication and then you told me or my IRB, well, we're looking for these patients, but ultimately a lot of them are going to end up getting excisions, I don't think I'd even get to come to the meeting about the approval. I'd be interested for Ms. Knudson's --

MS. KNUDSON: I think you're absolutely correct. They're either not surgically possible patients or they are.

DR. STERN: Could you clarify that for me then?

DR. HESTDAL: I can clarify a little bit how the thinking about that is. We have done low-risk nodular BCC and superficial BCC, and we see that in the case of surgery, the sustained response rate is lower. So we think that if the patient wants to have or the doctor thinks that cosmesis, for example, is one feature that is important for

the patient and the patient should have this option to not have surgery, that's one point.

The other thing is that we think we have provided evidence today that shows that we are similar to cryotherapy. So you use cryotherapy in a lot of your BCC treatments. We heard also the other speaker here say that that was the case.

DR. STERN: So perhaps this is semantics. Then do you mean where surgery is not desired as opposed to desirable?

DR. HESTDAL: Yes.

DR. STERN: Okay. That's a very different thing in terms of who it might be used in.

DR. BRAATHEN: We have in our department several years of experience with this treatment, and there are a number of patients who because they don't want scars on the face and so on, and because you can use this treatment practically in an unlimited number of times and you still have the other options. So you keep open all other options, and if you heal them with the PDT in the beginning without any scars, the patients are very happy. So that's the rationale of all this thinking. And in the clinical setting, I think we have to agree that the patients more and more are looking at the cosmesis.

DR. STERN: I'm sorry. The sponsor hasn't used

its 10 minutes. Did it have additional things it wanted to bring forward?

DR. HESTDAL: That's right. So then we also have in regard to the skin sensitization -- maybe Lasso can come back.

DR. BRAATHEN: My name is Lasse Braathen. I said that previously. I'm educated in Germany and in Norway. I have three specialties, dermatologist, allergology, and clinical immunology and angiology, and I also have a master in health administration.

The FDA is curious about the unusually high rate of sensitization. If you look at what is around in products over the counter, you will see that a lot of these products contain parabens. Benzoyl peroxide, for instance, is an over-the-counter drug here in the States I think. Benzalkonium chloride. And if you submit these substances or these over-the-counter preparations to the kind of procedure which has been done in this sort of guinea pig maximization test, then I think you would get sensitization in most of them.

The second issue is what is the problem of sensitization. I have treated probably, my own patients, about 300 or 400 treatments, and a lot of them are repeaters. They come regularly for treatment because it pops up new and it's mainly actinic keratosis but also

occasionally basal cell carcinomas and Bowen's. In our department, we have treated more than 2,000. We have not seen one single case where we suspected a contact sensitization.

Now, a phototoxic reaction does not give papules, does not give the vesicles unless you burn the patient. A photoallergic reaction or an allergic reaction is defined as T cells which are specific for the particular antigen and it spreads. We all know that if you test it, it spreads outside. I've never seen any cases where I even got the idea that there's an allergy behind it. All have typical phototoxic reactions and it's like sunburns. That's my clinical experience.

Now, the second thought is, does it really matter. We use drugs which induce immune reactions. We use diphencyprone which is an obligate contact dermatitis antigen for treatment of alopecia areata. We induce on purpose a contact allergic reaction in order to treat the patient.

Secondly, a new drug which is now coming is imiquimod which acts over the receptor 7 and induces an immune reaction, a very strong immune reaction. You have to treat the patients for 3 months, and the patient is going around with heavy skin inflammation for all that time and we are happy when the lesions then clear at the end.

So to me I don't think it's really an issue. If there is some contact dermatitis in addition to the free oxygen radicals -- it's even also described apoptosis in the lesions -- then I think I would be happy if there is an additional thing going with the rash which is helping us to cure the patient.

Earlier today, the question was how far down in the skin does the red light penetrate. It's about 5 millimeters.

Another question was the time for the freezing and we have the data now. It's 35 plus/minus 12 seconds. The range was 20 to 90 seconds and the median 40 seconds. I guess that the reason for this, they're all experienced clinicians, and you know, as well as I do, that everybody does the freezing in his own way.

I believed, when I was younger and until I saw these studies, freezing studies in actinic keratosis, cryotherapy, that cryotherapy was 100 percent until we saw the results of the prospective study. We also all know we have to admit that. I'm certain that Professor Stern also will admit that. I would never allow a publication out of my department that showed that my basal cell carcinoma treatment results were much less good than what was the average. I would then not publish. So what we see as published data are mostly from people who are very proud of

their results and with right because the data we saw here today of recurrence rates with different methods are superb, but there is no incentive to produce or publish bad results. And we know it.

So, in effect, in our department we use this as a routine method for actinic keratosis and for selective cases of basal cell carcinomas, and that is these cases where we try because of the cosmesis. It may be on the eyelid here and also here where we then see this is going to be a major surgical thing and the result is very unsure. So let's try something else first which we know has a very good cosmetic result.

Thank you very much for your attention.

DR. MURRELL: There was one more answer to your lower leg question. Because in the high-risk studies, the patient's locations were coded by extremity, face, or scalp or trunk, I can only summarize for the extremities, but there didn't seem in our studies that there were many of these large lesions on the upper limb. They were mostly the lower limb, but I'd have to go back, get the CRFs out to tell you specifically below the knee.

But there were 30 extremity lesions in the 310 study and 91 percent complete response rate at 3 months when the biopsies were taken. 18 of those were characterized as superficial lesions, and 17 out of 18 were

complete responders, 94 percent, and at 2 years, 2 out of those 17 had recurred, with a 12 percent recurrence rate.

In the 205 study, there were 6 superficial extremity lesions. I don't have the total number extremity lesions, but 5 out of 6 had responded completely at 3 months and at 2 years none of those admittedly small numbers, 5 had recurred.

Thank you.

DR. STERN: I think we're once more open for committee discussion, and I think it was Dr. Ringel's turn for her questions 2 through n.

(Laughter.)

DR. RINGEL: Hopefully we won't get to n.

One thing that I think would help me is actually to see this kind of in progress. We're talking about if there's an allergic reaction, if there's a phototoxic reaction. Do you have any pictures of what this looks like the day after, a week after? Do we have any clinical pictures with us so we could actually lay our eyes on this thing as it goes through?

DR. HESTDAL: Sorry. We don't have them with us.

DR. RINGEL: Another issue was on page 52, figure 9, you have a nice picture of histology versus the penetration of MAL into the basal cell carcinoma. One way

to address the penetration -- we don't really care so much -- well, of course, we do -- how far it goes into the skin. I think people are concerned does it go into the skin enough, and more important, does it go into the basal cell carcinoma enough. Have you tried to do any studies which compare lesion depth to percent penetration? In other words, will it penetrate a 3 millimeter nodular basal cell carcinoma, a 5 millimeter, a 7 millimeter, that sort of thing?

DR. HESTDAL: Did you ask if we have looked for penetration?

DR. RINGEL: In other words, if you have a very deep basal cell carcinoma, what's the maximum this will penetrate? Will I be able to treat a 7 millimeter deep basal cell carcinoma or a 10 millimeter deep basal cell carcinoma? Do you have any data that compares depth of penetration of MAL to the lesion depth?

DR. HESTDAL: We have looked at the data in 307 and 308 in regard to the depth before including the patient and then the results. I think one of the studies showed that there was no -- I think we have the lesions up to 5 millimeters in depth and there was no difference in response in the different superficial or nodular.

The other thing is that we have looked at the penetration depth in regard to measuring photoactive

porphyrins. In this study no nodular lesion was larger than 2 millimeters in depth, but we achieved this 98 percent relative penetration depth. So both clinically, as well as with the fluorescence measurement, I think we have data that indicate that you can treat pretty deep lesions.

DR. BRAATHEN: Maybe I could add. There is guidelines for photodynamic therapy which is given by the British Association of Dermatologists. It is now published in the British Journal of Dermatology. And they conclude that they recommend that lesions up to 3 millimeters can be very efficiently treated with PDT.

There is a way to solve that problem. If you have a lesion which is thicker, you debulk it and you stop the bleeding and then you apply the cream.

DR. RINGEL: And the last question I have is back to the data from one cycle of treatment, two sessions, but one cycle. I have many patients where I do the biopsies and they don't come back because, as far as they're concerned, it looks so much better. It's very hard to get them back to the office. It's going to be even harder to get people back to the office who have two treatments of this 3 months later. There are going to be a lot of people who are going to get lost to follow-up.

So I was wondering, once again, I know the FDA didn't have the means to have any data on this, but perhaps

in some of your earlier studies, do you have any data of what kind of cure rates you got after one cycle of MAL-PDT?

DR. MORRIS: I don't think that the studies have been generally designed to look at one or two treatments.

DR. RINGEL: It felt as if you must have had a reason to do two cycles rather than one cycle because obviously you didn't feel that there was a sufficient cure rate for one.

DR. MORRIS: Yes.

DR. RINGEL: So I was wondering what the data was --

DR. MORRIS: We realized from the phase II data that about a third of the patients, roughly, had to come back for a second treatment, and that has been shown again in the phase III studies. Roughly, but I don't have exact figures here.

DR. STERN: I think Dr. Katz was next.

DR. KATZ: Are you finished with your questions, Doctor?

DR. RINGEL: Yes, I am.

DR. KATZ: On this DVD, was that an actinic keratosis treated or a basal cell carcinoma? We were given this DVD. We were given a demonstration. It was very well depicted.

I have some comments because I'm a practicing dermatologist. I see maybe an average of 400 basal cell and squamous carcinomas a year and actinic keratoses at every hour. To think of having a patient come and wait 3 hours and put medicine on and then treat it with this machine, when I can spray -- and yes, I always tell people, as artful as we are, we do get an occasional white spot. But it's astounding to me that that would be done.

The other question I have, amongst others, Dr. Hansson, that first slide you showed of the patient who had a recurrence after Mohs, how many patients have you treated with this therapy with Mohs recurrence like that?

DR. HANSSON: I don't think it's correct to call this particular patient a recurrence after Mohs surgery. This was a patient with a very large lesion, as you saw, on the nose where they started Mohs surgery, but because of excessive bleeding and problems with anesthesia, they couldn't finalize it.

DR. KATZ: I see.

DR. HANSSON: And as an alternative, in this particular patient, the primary option was not possible, and since we, at the same time, were doing this study in Australia on difficult-to-treat or high-risk basal cell carcinoma, this patient was then included in that study.

DR. KATZ: Thank you.

People alluded to patients not desirable for surgery on anticoagulants. I think the literature is now quite adequate in the last couple of years that patients on an anticoagulant -- one study specifically in Mohs surgery, that was no problem and they had no problems with aspirin as well. Those studies are in the literature. We have worried about that for years. The standard was to call the internist, ask him to take off the anticoagulants for a couple of days, but now we know that even deeper surgery in the general medical literature can be done with anticoagulants. So I think that shouldn't be used.

I think we should not spend too much attention on the cosmetic issue because obviously if you have a treatment that gives a much poorer result, you're going to get better cosmetic results. In other words, if you have after 3 months a 47 percent treatment effect at 3 months rather than a 95 percent at 5 years, obviously you're going to have a better cosmetic result because you're not getting rid of all those other tumors.

The other point was the big point not getting hypopigmented results. But on page -- if I can find it. The slide on the person's back. What page was that? I had it flagged. 124. I have no criticism of the photograph. No, it's not 124. It's the person's back in the red book. Right, thank you.

That picture to the right is fuzzy. I have no criticism of that, but if one looks closely, you can see four hypopigmented areas. Obviously that's no criticism of the treatment because if you treat adequately, you're going to get post-inflammatory hypopigmentation no matter how you get rid of the tumor. If it's extending down, you're destroying dermis. So I don't think the cosmesis should be a major issue.

Many of these lesions are treated and a lot of time is spent taking care of these patients where a simple surgical excision with -- I think it's pertinent that the bias -- and we have Dr. Bigby here -- against negative studies -- I agree, they're not published.

But we clinicians rely on some statistics, and then you figure in your own mind how many basal cells you treat and if you try to be self-critical and you think how many recurrent basal cells have I seen in the last year -- now, true, many patients won't come back, but we still would see recurrences that colleagues have treated. So the recurrences that don't come back to see me, on the other hand, I would see colleagues'.

Generally speaking -- and I don't have any hard data -- also speaking to colleagues in my own journal club which has been going for over 30 years -- and it's informal, so we're very self-critical. It generally hangs

in there as indicated by the literature. You get about 5 percent recurrences.

Now, that's because you're referring patients who are not appropriate to what we're doing. I don't do Mohs, and I don't do extensive plastic surgery. So that wouldn't correspond to where surgery is not desirable. Just because I can't do the surgery, that doesn't mean it's not desirable. It's a very simple thing in this world to refer people where it's most appropriate, and if we can't take care of it, then Mohs.

And the general results that Dr. Rotter gave with 1 percent recurrence, 1 to 2 percent repeatedly occurs in the literature, and if I think of the recurrences that I see relative to the people that we refer to Mohs, it's in that ball park. It may not be exactly that. It might be 3 percent. We're talking about figures like that, and here you're talking about a complete response rate of 47 percent on that other slide that we were discussing, 2-year complete response rate of 9 percent, if you eliminate the people not showing up, and 34 percent if they include those as failures compared to 16 percent in the surgery group. That's at 2 years.

The article referred to in the FDA document showed -- I forget the number, but only 50 percent of the people who are going to have recurrences show up at 2

years.

So we're talking about certainly a treatment that is better than placebo, but in practice, if you offer it to a patient a treatment that was better than placebo and they'd have to go through all of this, wait for 3 hours and have two treatments, come back in 3 months for another trial of two treatments, I'm sorry. I mean, with all due respect -- and I do respect and appreciate our colleagues from Norway coming. With all due respect, it's very insufficient. If I landed on this planet now, instead of having 35 years of experience, and somebody showed me this treatment with this light and then somebody else said, yes, but I could just cut it out or even the most extensive thing we'd go to is Mohs surgery and you've got to be around for a couple hours, I'd say we've made an advance in 200 years. And when I say 47 percent, that's not including Dr. Alosh's statistics which really decrease that cure rate.

DR. STERN: I'm sorry. A representative of the sponsor wanted to make comments.

DR. MURRELL: Just in response to the 3 hours, about how the patients react to that. In the studies, what we normally have done is have the patients come in for a short while to prepare the lesion and put the cream on. At least in Australia, our patients then go off shopping,

spend the 3 hours. They don't wait in the hospital. They go off and do something they want to do, and then they come back 3 hours later. So they're not usually waiting in the office for that time.

DR. STERN: Jimmy.

DR. SCHMIDT: I guess I'm really unlucky to have landed in Houston and worked at M.D. Anderson because I really think that some of these bleeding problems that you see with some of these patients with cancer, as Paula can tell you, are a very serious problem. I realize the simple patients that you might see you wouldn't worry too much and you wouldn't even stop the anticoagulants. But we really see some absolute horror shows two and three times a day even. I really think we need something else. Of course, I think we have good radiotherapists too where we get a small recurrence rate. But I don't know. I think that this thing about the bleeding -- I think that there are some real questions here, when you're in a situation like some of us are, that we need some of these things.

Paula, do you have a comment on that?

MS. KNUDSON: I understand exactly what you're saying and I certainly had our dermatology people reporting a lot of adverse events with a lot of bleeding on their cancer patients. I don't really know anything about radiotherapy, however.

DR. KATZ: But there is data. There are studies with Mohs with patients on anticoagulants.

DR. BULL: I think we need to keep our discussion focused on what's in the application.

DR. STERN: Exactly.

DR. BULL: That's a context that has not been studied.

DR. STERN: The application and the data that support it, as I understand, are for the treatment of -- I'm using the word "primary," that is, nonrecurrent superficial and nodular basal cell carcinoma, and it doesn't get into the issue of --

DR. WILKIN: I guess this is actually for the sponsor. I thought I heard them say today they're not seeking high-risk. So they would exclude. It would maybe be rewritten in a way that it would actually say maybe low-risk.

DR. MORRIS: Yes, that's correct. That's also the indication that we have in the other countries where the treatment is approved where it's for treatment of basal cell carcinoma where other treatments are not suitable, and in Australia, where surgery is not appropriate.

DR. STERN: Well, that's, the way I hear it, not exactly the same thing. To my mind, although I don't like the terminology "low-risk" because one can think of

low-risk in a whole variety of ways -- what are the chances of recurrence, how large is the cosmetic defect likely to be from it. There are a whole variety of parameters that go into the risk of a tumor in an individual beyond their underlying health state and anticoagulation.

But what you've said, as I understand it, you're basically approved for tumors where, shall we say, the more conventional therapies are generally not thought to be appropriate. And what I understand is in the studies that we've seen today, the subset being treated are exactly the patients for whom other modalities are appropriate. So once more, I bring up, at least in my poor mind, this disconnect between the data we have and what the relevant characteristics of the patients studied are versus the fogginess in my mind about what indication is really being sought at the end of the day.

DR. MORRIS: We did face, in a way, a dilemma when we were designing the clinical studies because we wanted to have excision as the endpoint since that is what we agreed on as an appropriate endpoint to determine the outcome. We also wanted to compare to conventional therapies. So we needed to do studies on patients where surgery was appropriate, but on the other hand, we have also included these other studies where surgery is not so appropriate in some of these patients as supportive

evidence.

DR. STERN: Do you wish to make a final comment?

DR. LUKE: No.

DR. RAIMER: Well, my comments were a little bit similar to Dr. Stern's. The trouble I'm having is it seems that for a small nodular basal cell carcinoma, that this treatment is clearly inferior. But as a clinician, I would really like to have it for large superficial basal cells on the legs which are very difficult to treat. You have to excise and graft. There's a lot of morbidity. For the patient we saw on page 125, the large fairly superficial-looking lesion on the nose, it seemed to work well. I mean, I would like to have it for that sort of patient. That's not really a low-risk patient.

Are we allowed to consider like in European countries the indication for lesions that are not appropriate for treatment --

DR. BULL: I think when we get to the questions, because I think you also have to address the sufficiency of the data in the application. I would not be swayed by the fact that a few pictures were included in the submission and be persuaded by that. I think you also have to look at the numbers, the quality of the data, what the comparators were, and to make a decision or a

recommendation that's based on data that you can deliberate in a way that provides sufficient context for a recommendation on a particular subset of patients. So I think that that may be something that you can look into as you move into the questions. Whether or not there's sufficient data in this particular submission to substantiate that as a claim I think is entirely another issue.

DR. STERN: Dr. Bigby and then Dr. Tan.

DR. BIGBY: This is just a question about the procedure. Is the amount of time that the light is shown determined by sort of metering the milliwatts per centimeter squared at the surface of the patient at the time of treatment and then you calculate how long the light should stay on?

DR. MORRIS: Yes. The lamp calculates how long the time should be to deliver the dose of 75 Joules per square centimeter, which is the total dose to be delivered.

DR. BIGBY: Based on some measurement taken at the surface?

DR. MORRIS: Yes, because you set the size of the diameter of the light field and then you have to calibrate and see the intensity of light that you have at the skin surface using that distance, and then the lamp automatically calculates the time and it will turn itself

off.

DR. BIGBY: But is that just based on the diameter and the distance, or you actually meter the surface?

DR. MORRIS: We measure it with a probe.

DR. TAN: I just want a clearer mind on the assessment of response rate. For the two pivotal trials, at the end of the 3 months, you have the complete responders. For those patients that will remain to be clear at 6 months. Right? Is that true or not so? In other words, those patients who are complete responders don't have a recurrence within 3 months, the follow-up of 3 months.

DR. PARISER: The number 6 months was 6 months from enrollment.

DR. TAN: So one patient has responded. At the end of 3 months, he's a complete response. In another 3 months -- so that's the end of the -- that's at 6 months. Right? And at 6 months, when you look at this patient again, does this patient have recurrent disease or not?

DR. PARISER: No. Every patient is examined 3 months after the last cycle of their treatment.

DR. STERN: Dr. Drake?

DR. DRAKE: I just want to compliment the company for tackling this very difficult area and this very

difficult subject to study. I can tell you, we have precious little data that's adequate in my opinion in any area of treating skin cancer. Maybe it's because I'm biased because I've been at tertiary referral centers my whole career, but I tend to see what other people think they've gotten rid of and it tends to show up at our place in many instances.

I don't think we have good tracking. There's no tumor registry. I chaired an NIH panel on outcomes for non-melanoma skin cancer, and in fact there are no registries for non-melanoma skin cancer. We don't have any way of really tracking any of this in a very sufficient manner. I think the data is weak in general on what really happens to skin cancer.

So I want to thank the company and the FDA both for trying to make some sense out of a very difficult subject. So I wanted to say that as a header because I think the panel is trying to hang numbers on things and rely on these numbers, and in fact, these numbers maybe are not the best. But guess what. They're at least an addition to what we know, which is in some respects not adequate.

Now, I tend to agree with some of my other colleagues. I think this is a niche product. I think this potentially has a role for a subset of patients that we

need something for. I agree with the big superficials on the lower legs on diabetics. I agree with people who are on anticoagulants because I think these are problem patients.

I also think there are some patients who just, due to a variety of reasons, really don't want cold steel surgery, and if you have something less invasive and less problematic to offer them, they might be very grateful for that opportunity. I've seen C&Ds done by doctors who are superb and get superb results. I've also seen C&Ds done by people who don't get any kind of decent results and you have really nasty recurrences. This in fact might be helpful to those people. If they don't know how to do a C&D, perhaps using light and a photoactive drug, a PDT therapy, might actually help them get the tumor that they can't seem to get with a C&D.

So I'm going to speak for this. If we approve it, I certainly don't think that there ought to be broad claims or broad indications or broad anything. I think it's a niche drug, and I've seen this committee approve niche products before for a subset of patients where something may be needed and this is something new that's come along that might be useful in that arena.

DR. STERN: I think we're about ready to move on to the questions after Dr. King, and I'll perhaps ask

one final question.

DR. KING: I have to be agreeable with what Dr. Raimer said and Dr. Drake said, that there's a great deal of empathy, having practiced both now in the VA and the tertiary care and now in a private practice type setting, that there are patients who, for a lot of reasons, need a niche product.

My other point is that, on the other hand, once you open Pandora's box or, in the South, a can of worms, once you put something out there that's FDA-approved, how are you going to ensure that non-dermatologists are going to do skin biopsies or have the ability to follow it up? It's been my experience with laser, which has an enormous complication rate in Nashville because everybody has got something where if you shine the light on, you're going to open up the pocketbook, that people buy these things and use them without a great deal of training. So I guess my concern is how would we write the PDR or the instructions about who's to use it and how to use it and how would the insurance agencies or Medicare view this when simply sometimes it's instruction by any means.

So I'm favorable for niche and then I'm worried about, yes, but if you put a gun in the hand of a 4-year-old it's different from a 40-year-old. So we should be very careful about how we define the issues here: niche

versus broad-based.

DR. DRAKE: Lloyd, I want to respond to that. I think you're right. But we have other things out there that used in the wrong hands by the wrong people cause lots of problems, and that hasn't stopped us thus far. So I think we ought to think about how carefully -- Lloyd, you're exactly right -- can we write the labeling and how cautiously can we do this so that it's used appropriately. You can't regulate behavior all the time, but what you can do is you can try to give people an opportunity to understand how something is to be used and hope it helps some patients because my bottom line here is are there patients that this product might help. I think that's where my goal is. Is there a subset of patients where this might be a useful product?

DR. KING: My back-comment is if 40 million people do something dumb and stupid, it's still dumb and stupid.

(Laughter.)

DR. DRAKE: Lloyd, how many dumb and stupid things do you see done every day with stuff that's already approved?

DR. KING: A lot.

DR. STERN: I would hope that we would stay on both the evidence and the indication. I guess before we

start the questions, I would like to share another way of how I've synthesized these data, and that is, what would be informed consent for a person with a small nodular basal cell carcinoma coming to my office who is perfectly healthy, not a niche, basically eligible for these trials? So how would I express this on the face relative to the other therapies available? And let me tell you how I would have to do it, as I synthesized these data.

Well, I can send you to the Mohs surgeon. It's going to take a half to a full day of your time. The chances of recurrence after that are 1 to 2 percent. Unless it's a big tumor, in which case you really needed it, you'll have a good cosmetic result. If you have a big defect and a bad cosmetic result, it means it was good that I sent you there. It was one of these so-called iceberg lesions. So that's one possibility.

I can send you to a skilled surgical colleague, be they a dermatologist or a plastic surgeon, and they'll excise it. It will take 35 minutes and you'll have an excellent cosmetic result. The recurrence rate at 5 years might be as high as 5 percent, although the person I use is much better. So since I think it's an appropriate lesion, it will be less, but I'm just joking when I say that part. So that's the second option.

Or you can have me, who doesn't remember to

press the button, do it, and I can do it in two ways. I can do it with curette and electrodesiccation which will leave you a depressed scar. If you let me leave a big enough one, I'll give you the same recurrence rates. If you want a smaller scar, the recurrence rate will go up because it depends on borders. Or I can do just cryosurgery and probably the same recurrence rate, and you'll have a white mark, a flat, macular scar in most cases that will be red originally, and probably a slightly higher recurrence rate. And we can do that in the next 10 minutes, but you'll have oozing and you'll have to take care of it for 3 or 4 weeks, but in fact you can do anything that you could do if you had gotten a scrape falling off your bicycle basically in terms of postoperative care.

So those are the available options.

Then I have this new option. The way I read these data is the other option is, as opposed to the half-day, one-time, and a suture removal, the 35 minutes, and a subsequent suture removal, I can send you for what on average will be three visits which will require for someone to scrape the lesion, apply it, have you return 3 hours later that day for irradiation, then after two treatments a week apart, wait 3 months to see if it's really working, to see if you need two more treatments a week apart, each

time, scrape, apply the medicine, wait 3 hours. In addition, on the basis of my synthesis of all the available data compared to Mohs, the chances it will come back are certainly at least five times higher and, compared to the other modalities, are likely to be at twice as high.

So that's the informed consent that I would have to give a patient in describing using this treatment for a small nodular basal cell carcinoma on the face. And you're right. I didn't mention any other non-approved chemical entities for nodular basal cell and I didn't mention x-ray therapy because we talked about it being a young, healthy person and that's not a good idea to do.

Now, if that's an unbalanced review for, as I understand it, the target audience who really cares about cosmesis, as I've heard, would someone tell me what went wrong in my describing our best information as it stands now?

DR. PARISER: Well, I'll take a shot at that, and you're right for the small nodular basal cell on the face. For the superficial or nodular basal cells on the lower leg where part of your informed consent for the C&D would be you may have a non-healing sore there for weeks, for your excisional, part of your informed consent would be you're going to have a big scar there, it may or may not be able to be closed without a graft. It does change that a

bit.

DR. STERN: How many lower-limb, below-the-knee lesions were in the randomized, controlled studies?

DR. PARISER: That's another issue.

DR. STERN: I'm talking about the evidence base and the application. We all wish for something that would take care of our problematic cases, but that's not, as I understand it, our mission here today to decide about this product for things we wish we could do better.

DR. PARISER: Specific numbers on the superficial --

DR. KATZ: Everybody is focusing on lower-limb lesions. When this destroys this large basal cell, doesn't it leave an ulcer? The lesion is being destroyed. You mean it just heals the next week magically or might it take 3 or 4 weeks? I cannot imagine a large basal cell, which we would all love to have a magical treatment for, that this goes away and epithelializes on a lower-extremity lesion.

DR. PARISER: Well, it certainly epithelializes or heals much different from cryo or from a C&D in that area in terms of healing time.

DR. KATZ: That's what I would suspect. So that's the point. The point is where these folks are looking for wonderful treatments for lower-extremity

lesions, like Dr. Raimer and myself included, this is not inferior or superior to that unless you get a higher recurrence rate. If you're going to get a higher recurrence rate, which we do have, it's going to heal much faster with this treatment because you're not treating as much of the cancer.

DR. BRAATHEN: Of course, the chairman is right in his description of what do you tell the patients.

Now, if you have a patient with cancer, you have biopsied it and you say, you have a basal cell carcinoma and we have to cut it out, but there will be scars, the patient will say to you, it doesn't matter as long as you remove it. If you give the patient the option, as you so nicely described, and said, there are several treatments, there is one treatment which gives less scars than the other ones and less complications -- there are published studies also on cryotherapy which show more complications -- but which gives you less scars and in case it recurs, we can do the treatment several times, and we still have all the other options open, that's what I tell my patients. And most of my patients, if not all, jump on the PDT. They want something which gives them less scars. I think I'm doing my job then by giving them this treatment.

DR. STERN: Dr. Wilkin.

DR. WILKIN: Yes. First of all, I think in Dr. Drake's lexicon, she calls it "niche," and we think of them as somewhat well-defined indication groups. But however you want to call it, I think we are interested in knowing if there is that segment of the data that might support that. And along that line, Dr. Katz actually mentioned would we have data for superficial BCC, recurrence data. I have to tell that the agency was not relying heavily so much on this because we were approaching this from the construct of first one achieves nodular and if there's success in nodular, then we'll look at the superficial BCC data.

But we do have a slide. It's by patient recurrence and perhaps the sponsor has some way where they can break out the recurrence data for superficial. I think that would be directly responsive to Dr. Katz, but in the meantime, we could show our slide 18 and the additional slides.

Actually in the sponsor's document on page 110, table 65, they have lesion recurrence rates at 12- and 24-month assessment. This is the agency's evaluation as a patient recurrence. I think the notion was if there are several of these superficial BCCs, a patient would come in and get all of them treated. So we were interested in the analysis of whether the patient would have to come back.

But these are the sponsor's data on page 110. This is ours. The sponsor may want to speak to this. It's in the interest of what Dr. Drake was mentioning about the niche.

DR. STERN: Would the sponsor want to comment?

DR. FUGLERUD: Yes. This shows the patient recurrence rate after 12 and 24 months, and a patient was defined as a recurrent patient if at least 1 of the lesions within the patient was recurrent. So it was categorized as recurrent if at least 1.

The corresponding lesion recurrence rate after 24 months was 17 percent in the MAL group compared to 20 percent in the cryotherapy group.

DR. STERN: Thank you.

DR. HESTDAL: I think we have today shown the sustained response of both cryotherapy and MAL-PDT in the same studies. Is that what you would like to see?

DR. WILKIN: Well, actually it's for the committee for their deliberation, but I thought what you had was a way of looking at the recurrence rate for superficial after your modality. Again, I thought it was on page 110 in your briefing document.

DR. FUGLERUD: I think it's table 65 in the briefing document. It's on the screen also. So it's the recurrence rate after 12 and 24 months, and that's the

recurrence rate calculated among the lesions in complete response after treatment. So in the MAL group, it's 108 lesions and in the cryotherapy group, it's 94 lesions, and the recurrence rate after 24 months is 17 percent in the MAL group compared to 20 percent in the cryotherapy group.

There's 7 percent missing in the MAL group compared to 5 percent in the cryotherapy group. So the recurrence is calculated without the thing missing as recurrent.

DR. STERN: I'm a little confused in how there are 8 missing. When you exclude missing values, it goes from 108 evaluable lesions to 91, and where I come from, that's a difference of 17. I just don't know how 8 and 91 get up to 108. So could you just clarify that for me?

DR. FUGLERUD: Yes, I understand the question that the missing value column is a little --

DR. MORRIS: In the life table that we showed you this morning, we have this data. We can find it.

DR. STERN: It's not really essential. It's just I got confused.

DR. FUGLERUD: Yes, I understand. But can you take this back again, this table?

I agree that there is a mismatch between this 108 and this 8 missing, so we will check this. But the calculation handled as missing is in the second column and

in the fourth column.

DR. STERN: Does anyone have an extremely pressing issue that they don't believe would be covered as we go through the questions?

(No response.)

DR. STERN: Good. So why don't we move on to the questions, which I'm sure, since part of the questions are likely to elicit questions, may help and direct us to the specific reasons that the agency has turned to us for advice about this application.

So question 1 is: The investigator's manual included the following lesion preparation instructions for use. "Tumor fragments from most lesions may be removed without damaging normal skin and without use of anesthetics." And here the question is -- I think it should be, was lesion preparation instruction adequate to ensure sufficient consistency among operators?

DR. WILKIN: That seems to invite a yes or no response, and what we would really like to hear is something more than that. We would like to understand if more might be added to this to make it understandable and helpful and consistent with how this was done. I think we heard, at least I heard for the first time today, from Dr. Pariser the phrase "curettage and lesion debulking," that that was the understanding that the investigators had. But

we're looking for what we might craft into labeling.

DR. STERN: I guess I'd like to start with a couple of comments. One is -- I'm sorry I can't find the page, but in the illustration of curettage that's in your diagram, it didn't like you were instructing individuals to basically take off what was above normal epidermal level. In fact, the way it looked to me is the instruction was to go below because it looked like there was supposed to be a depression, an erosion or ulceration left afterwards.

Secondly, where I come from, when you're trying to put forward a therapy, I always show my best results, and at least on page 123, the pre-application, post-curette slide showed to me what looks like my usual kind of first-time curetting.

Oh, I'm sorry. We can't discuss with you anymore. We can only ask for clarification.

So to me that, combined with what was pointed out, was heterogeneity in fact both in the controlled studies -- both within the sham group that got curettage and the treatment group, there was tremendous center-to-center variability between centers for both. If you looked at what you could perhaps attribute to curettage alone and you looked at the cure rates there, in some centers a large proportion of tumors were cured without the aid of an active MAL-PDT basically, without the MAL part of your PDT,

a sham PDT. So that to me suggested that it's either patient selection variability or in fact variability among operators and what they did or perhaps evaluators in what they took to be a recurrence.

But certainly when you go from 0 to almost complete cure rates with small numbers, it suggests that not everybody is either treating the same patients, looking at them afterwards in the same way, or doing the same thing in the control group, which suggests that even among trained investigators, that there's heterogeneity in the interpretation of the results in the investigator brochure. I think we need more direction if it's going to be labeled.

DR. BULL: I just wanted to remind that given that we're in the question part of the meeting, that the questions are directed to the committee. You're beyond the point of clarifying. You have to basically deliberate based on what's been presented and discussed.

DR. STERN: Ms. Topper just informed me in capital letters about that.

Each individual who has comments about this should make them. I think what we'll do is start with the voting members of the meeting, and if Dr. Plott has something particularly pressing, we'd love to hear his comments as well, but he's non-voting.

DR. RINGEL: In brief, I agree.

The only other comment I could make is that we also heard that the company really didn't feel that they could count on MAL penetrating more than 3 millimeters into a lesion. Therefore, they should be curetted, rather than just superficially abraded. It sounds like a nodular lesion that you think may be very deep really should be curetted, if that's truly a concern for them, and I think it should be standardized.

DR. TAN: Yes. I just want to add maybe you should use some kind of range. Instead of giving a firm limit, 3 millimeters, maybe 3 to 5. I don't know. That might be something worth considering.

MS. KNUDSON: As I recall, somebody said that curettage was not supposed to be a therapeutic curettage. Would that be language that all dermatologists would understand, that you would not be doing a therapeutic curettage when you're doing this preparation?

DR. STERN: This one wouldn't.

DR. KING: I guess I think about this as more like curettage and photodesiccation. Being a dermatopathologist, I'm on the other end of this. So what you see in, say, 10 dermatologists is 14 ways of what you get. So I would like, if they could do that, standardize it, but as a practical matter, I doubt if you will. Maybe perhaps you could talk about slicing with a razor blade so

that you don't cause pain as opposed to taking the razor blade made into a curette and dragging it across there. So I wish I could come up with a standard way, but I'll tell you from practical experience it's going to be very difficult.

DR. KATZ: Is this for discussion or yes or no? It sounds like it's discussion.

DR. STERN: Your opinion about more specific instructions and standardization are needed should this product be labeled.

DR. KATZ: Obviously it was curetted sufficiently that 33 percent of the people didn't have any lesions. I don't think I agree you're not going to be able to tell somebody exactly how much. It's incredible to me that bleeding wasn't present and people had no pain by the amount of curetting because 33 percent were cured. But I guess it should be better standardized, but I don't see how it could be in defense of the sponsor. I don't see how they would be able to say curette only very little.

DR. SAWADA: I have to agree with Dr. Katz. I can tell you that the limiting standard for curettage is going to be my patient's pain factor or perceived pain factor. It would be very difficult to figure out a way to standardize millimeter depth that you need to take off of the basal cell. So I really don't have any good

recommendations as to how to standardize that for the insert.

DR. STERN: I'll make one other brief comment in terms of direction. It seems like the evidence we have is without a great deal of information about local analgesia. This is probably my own misperception but sort of an advantage of this is doing it without Xylocaine. As I recall from the old days of a variety of PDT-like agents or agents that give acute phototoxic reactions, as does methyl ALA, that including myself, although I've never used ALA, it burns like mad when you're doing it. Now, perhaps your patients are more stoic than I am, but it happens with tar, with UVA. It happens with almost any phototoxic agent that you're giving in this short period of time, enough of a dose to get the kind of result you've had. Maybe this ALA is different and we won't go there.

But I wonder whether -- at least my patients, you can barely get a curette near them without them wanting -- I don't ever curette someone, even superficially, without Xylocaine anesthesia. I mean, I think that would be considered outside the standard of practice in at least Boston. So I wonder if part of what might be helpful are really for the committee to consider whether in helping to standardize this -- I mean, I hate to have the standard being curette till they yell.

(Laughter.)

DR. STERN: It's not good for the patient and not a uniform endpoint because pain thresholds vary so much. I do think we need direction and I wonder whether we really want to be going for an agent that is sort of implied, oh, good, you don't have to give local anesthesia.

DR. DRAKE: I'm not sure but what this question shouldn't come later in the discussion. The reason I say that is I think the preparation will be determined a little bit by how effective one thinks this product is and what conditions you have to make it effective.

Earlier I asked the question about how deep this particular light source went. Frankly, with a lot of PDT, the limiting factor is not the photoactive compounds that you can attach to your target. The limiting factor is how deep you can get light to penetrate through whatever mechanism you want to go through. For example, there's some very good potential PDT for lung tumors. The question is how do you get it into that area of the lung. There's some potential stuff on bladder tumors, but it's pretty easy because you can put the light source right up through the urethra and get the light right where you need it, next to the source.

So the preparation I think, if you're prepping a big, old nodular, you're going to have to debulk it

because this light goes 4 to 5 millimeters I think. Isn't that about right? So it's only going to go so deep. So you're going to have to think about the efficacy of the whole product before you begin to talk about how to prep it because if you've got a thick nodular BCC, you're going to have to debulk it.

And I'm with Rob. If somebody comes at me with a curette without anesthesia, I'm going to holler like a stuck pig. I don't want anybody with a curette after me without anesthesia. I'm a coward. So I think you're right, Rob. I think in some communities -- because we're from Boston and maybe we share that.

But I think your issue here is prepping the lesion for efficacy and efficacy means you can't have too thick a tumor or the light wouldn't get there even if you decide to approve this product.

DR. STERN: Sharon.

DR. RAIMER: I don't really have anything further. I think Lynn's point is good. You're going to prepare a superficial basal cell differently than a nodular basal cell. That's a very good point I think.

DR. STERN: And in your experience?

(Laughter.)

DR. RAIMER: I'd want Xylocaine too.

DR. STERN: I was asking our biostatistician.

(Laughter.)

DR. SCHMIDT: I never saw the lesion preparation instructions from the company in the first place to comment. But my feeling is that, yes, there should be some fairly specific directions or guidelines on this. But like I say, I would like to have seen the lesion preparation instructions so I could comment.

DR. STERN: This is not a question but a clarification. Wasn't there a pictogram somewhere in this red book, or was I hallucinating? I just couldn't find it. Just tell us what page.

DR. MORRIS: Yes, there is one and it's the same as the one that was in the investigator brochure. We also had a video that was distributed to all the investigators in the trials.

DR. STERN: I'm not talking about the facial one. The little pictogram. I just couldn't find it now.

DR. BRAATHEN: Page 21.

DR. STERN: No, no, not the facial one. I remember a pictogram.

DR. MORRIS: It was in the presentation this morning. Slide 44.

DR. STERN: Data overload. Thank you.

Did you have other comments, Jimmy?

It's a slide we saw during the day which I

confused. Slide 44 in their presentation.

Yes.

DR. KING: Relative to preparation, it seems to me that the indication to use it is the diagnosis of basal cell to begin with, and it seems to me that if we had the depth like you do for melanoma, saying this is a so-much thick or depth lesion, then the preparation would follow about whether you even have to debulk it to get what Lynn is talking about, how deep does it go. So that's why I was having the thought rolled up into curettage and photodesiccation. You really do need to know the tumor depth to know how far it's likely to go because your basement is still flooded. Your first floor is okay, but if it's still down in there, you're going to have to make the light go deeper.

DR. SCHMIDT: Just to have this little picture I don't think is adequate to ensure consistency.

DR. STERN: I believe you've heard from the committee the idea that information is helpful in guiding clinical practice about things that are intimately related to a drug and device. So you've got a triple header here. It's procedure, drug, and device that are all together.

So let's go on to question 2, which is a two-part question about efficacy. Please discuss the adequacy of outcome measures as well as the number of patients and

lesions to assess the efficacy of MAL-PDT in the treatment of nodular basal cell carcinoma for, first of all, 6 months post-treatment by histology only, not clinical, in two pivotal studies, no follow-up available; and then, B, 2-year clinical follow-up available in one open-label, randomized study and one open-label non-randomized study.

DR. WILKIN: If I could just make a quick comment. On the no follow-up available, that's not meant to be pejorative. This is where the lesions were completely excised. So it wasn't really meaningful to then look for recurrence in that setting.

DR. STERN: Yes. The one issue -- actually I'd particularly like to ask Lloyd King's advice about this -- is in looking at the 3-month excision, the question is, how good is breadloafing -- I guess there are two sequential questions, one particularly from a dermpath -- a breadloaf specimen. What is the likelihood it would have picked up a recurrence, should it exist at least histologically?

And the second is I'm not sure that even histology at the time of an excision necessarily proves that that tumor wouldn't have recurred so soon after treatment because, after all, these are tumors that undergo proliferation and it only takes one residual tumor cell to have a recurrent tumor.

But could you perhaps give us some idea of what

you think the sensitivity of breadloafing is for the presence of histologic tumor 3 months after a procedure?

DR. KING: Well, I'll actually refer to the presentation earlier for Mohs in the sense of vertical sections. You only look at about 1 percent of what may be a positive margin. Oftentimes for medical-legal reasons, you waffle and say the margins are free in the plane of the section. So that means you've got a 1 in 100 chance type thing.

In general, when we look at tumors like basal cells, you have a 10 percent error of artifact just cutting, say, 7 or 8 sections sequentially into the block. And if an experienced clinician calls it a basal cell and you don't see it or anything like a tumor, you call it the bumper. If they see a bump and you don't see a bump, you keep going.

Directly to the issue of breadloafing, you have about, in my experience, a 30 percent chance at the worst to about a 10 to 15 percent chance of missing small foci without immunoperoxidase with cytokeratin stains. As a matter of fact, the Mohs surgeons, when they're really nervous, send their specimens to us to do the immunoperoxidase to miss these small foci which may be thought of as, say, the root of a hair follicle or other kind of things. So they're indeterminate. Even with

immunoperoxidase, you may miss small foci. So I would think your chance of error is somewhere between 10 and 25 to 30 percent in breadloafing.

DR. STERN: Michael.

DR. BIGBY: Could the FDA just clarify to which studies are they referring in part B of this question?

DR. VAUGHAN: We're referring to study 303 for the open-label, randomized study and to study 205 for the open-label, non-randomized study.

DR. STERN: Shall we go around and start with you, Jimmy, about the adequacy of these studies to demonstrate the efficacy of this product for nodular basal cell?

DR. SCHMIDT: I thought that the numbers were small and the recurrence rate was high, but I think that it does show that there was efficacy in both of the studies.

DR. TEN HAVE: I agree. It sounds like it's more of a clinical debate as opposed to a statistical debate. The statistics basically say yes, there is efficacy. They've reached statistical significance. The question is are the differences that we see clinically significant compared to the costs of curettage and all of what else the photolight therapy entails. So it sounds like it's a race between cryotherapy and this new therapy in my mind.

And the non-inferiority trials. 303. Are they part B? Are the non-inferiority trials part B?

DR. VAUGHAN: The open-label, randomized study versus surgery was a non-inferiority trial. The one open-label, non-randomized study was just an open-label, non-randomized study.

DR. TEN HAVE: So 303 was with cryotherapy?

DR. VAUGHAN: No, it was not. Surgery.

DR. TEN HAVE: Oh, surgery. So you're not including cryotherapy here?

DR. VAUGHAN: No.

DR. TEN HAVE: Can I ask why?

DR. VAUGHAN: Because the indication in the studies were geared toward nodular BCC and based on the efficacy and safety of the nodular indication, then we would look at the one open-label study because usually we have one trial and then the study should be replicated by a second trial. The superficial was a non-inferiority study and that was just one study submitted.

DR. TEN HAVE: So it's basically the cryotherapy trial was not the right indication.

DR. VAUGHAN: Right. It was not one of the pivotal studies.

DR. TEN HAVE: It was not the right indication then?

DR. VAUGHAN: For how the drug was developed, it was not the indication we were looking at.

DR. TEN HAVE: So we're supposed to ignore it? Are you essentially saying we're supposed to ignore that cryotherapy trial for this discussion?

DR. STERN: Well, as I understand it, it wasn't of nodular basal cells. So since this question is about nodular basal cells and they clearly are different, as was the comparator therapy, I think for this question, we would certainly not consider that relevant data.

DR. TEN HAVE: So relative to the surgery, then it's not doing so well in terms of long-term recurrence rates.

DR. STERN: I guess I would ask the agency -- as I think you've pointed out very well, one could interpret this, does adding PDT to the regimen described have some additional benefit versus -- it clearly makes significance even in these small trials versus sham PDT and curette. Or are you asking it as you, I think, suggested? In a clinical sense, is this enough efficacy that you would, in fact, bring it up with your patients? Or do you have enough data to make a judgment that you would be comfortable taking these data forward to your colleagues and patients and saying, this is the situation with this and, in fact, it's worth entertaining, I'm confident of

what the data says, and the second part, it makes enough sense that it really makes sense to use? Which is the agency looking for? Or both?

DR. WILKIN: Well, here we're actually interested in the outcome measures, the adequacy of the outcome measures. Then we have a question that comes up next, which is has adequate evidence been presented to support, and then it says primary indication, but really we mean first-line therapy.

I have to say that we've approached the evaluation of this NDA with the notion that we would look first at nodular, and then winning on nodular, we would then look to superficial. That was sort of the algorithmic approach that we had.

I think what we heard today is that looking for a niche, which I think is fair -- I mean, looking at the overall data set and trying to make the assessment, but is there another way of looking at that? You could construct question 2 also to be in the treatment of, and then again, whatever niche indication that the committee would be interested in.

DR. RAIMER: To me the numbers do seem small to have a lot of clinical confidence in them.

DR. STERN: I guess, in terms of interpreting the data, I would take Dr. King in terms of part A, the

excision data, and say, well, I would expect that the true number of non-cured tumors would go up 10 to 30 percent in each group, and if they were different between any group studied, that means that the absolute difference between the groups would go up proportionately.

And I would say for the 2-year data, similarly, since we haven't seen any data to the contrary, whatever the differences are in recurrence rates, at 2 years we would expect that absolute difference to increase over time because all the data for every modality shows the same upward trend in recurrences as time goes by. So, if in general, at 5 years recurrence rates are about twice they are at 2 to 3 years, I'd expect both absolute recurrence rates to double, and therefore if they're different, the difference between them to increase by the difference between 2X minus 2Y, if X and Y were the first two recurrence rates. That would be my interpretation.

I think this is a small data set that I don't find particularly encouraging as something I would want to introduce in my own patient practice.

DR. SAWADA: Again, I agree with my colleagues in the sense that it's such a small data set. But the question is efficacy, and I thought it did show efficacy.

DR. KATZ: I think this question is not directed to whether we think the drug works or not. The

question is discuss the adequacy of outcome measures. So I think on this question -- correct me if I'm wrong, Dr. Wilkin -- it's not to give our opinion on how good the drug is or not, but how adequate the outcome measures are. Is that correct?

DR. WILKIN: In a word, yes. The timing and then also how one is looking.

DR. KATZ: So everybody has been discussing whether they think it's good or not or how they would use it, but on this, adequacy of outcome measures, it seems to me that they did adequate outcome measures. But that's to me. We rely on experts like Dr. Alosh. Dr. Alosh, are these the measures that you were discussing before statistically? You pointed out some inadequacies in it.

DR. ALOSH: Right. We presented the results for histology which is the sponsor's results, and then we looked to clinical and histology.

DR. KATZ: In these studies we're discussing right here.

DR. ALOSH: Right, the pivotal studies.

DR. KATZ: So I'd have to they're not adequate based on our expert opinion around the table. I think they tried to do an adequate job, but based on the doubts raised, we have to take that into consideration.

DR. ALOSH: Let me clarify. For the non-

inferiority trials, as I pointed out, really we did not put much emphasis on those because the protocol did not come to the agency for comment. I cited what I have seen as shortcomings in terms of there is no vehicle, there is no non-inferiority margin prespecified. For the pivotal studies, the results for histology, and then contrasted to the clinical and histology, you could see the response rate is lower.

DR. KATZ: So my answer would be, based on that, no to this question.

DR. KING: I'm struck, by thinking it through, that I guess you come from a bias of being a dermatopathologist that having a clinical is great, but last we heard, diagnosis of cancer is under the microscope. So I would have liked to have seen the clinical and histology on each one of them type thing in the pilot studies, and given the figure 4 where they're showing the tumor selectivity of the MAL cream, you wonder why at the time of, say, the second treatment, simply using a black light type thing looking to see if there are foci still there and then, say, doing a 2-millimeter biopsy or something like that because in the last 5 years, what we've been doing, we've been writing tumor BCC nodular, comma, with infiltrative at base. So you have 90 percent of something that's a nodular, scrapes like jelly. Yet, at

the bottom there are these things that look like the continent of Africa or South America. In hindsight, those are the ones that recur.

So I think that trying to define, in general, does it work -- how many of these are mixed tumor types because you can have superficial with a nodular component, you can have a basal with a sclerosing component, infiltrative features. So I would like to have seen that kind of thing rather than saying, oh, it's clear because at 10 years there are still going to be a substantial number of recurrences. Yet, you pull the slides back and all that and usually it's the lawyer sniffing around. The answer is yes, based on that particular section, it's all gone, but that's less than 1 percent of the total.

So based on what Dr. Katz said and I would say, I would rather have seen the clinical, the histology, and the simple add-on, doing the light at the time of second application to see why it may be needing a second treatment.

DR. BIGBY: Sometimes it just really gets to be very frustrating to me to hear things that are so simple become so difficult. Everybody here has already said there are more than 2 million cases of basal cell in the United States a year. So it's a common thing. It's not hard to find patients for this kind of study.

So what was presented in (a) really is a surrogate endpoint of whether this treatment compared to a placebo cures the patient. It's a surrogate because what they did is they took what was left in 6 months and they breadloafed it, and we saw that that is not an entirely sensitive method to determine whether or not they were cured.

So if you had unlimited resources and very smart people doing this, what you would really do is to do a controlled trial of the treatment versus placebo and follow them for 2 to 5 years, and you would really find out what the recurrence rate is after treatment and after placebo. So I think that the answer to this question of is the outcome measure adequate in section (a) is clearly no, and I don't think that anybody can conjure up an argument to make it so.

In terms of the outcome measure in the sort of part (b) section, maybe because what you have there is, at least in the surgical comparison trial, groups of patients who were treated and followed out over a period of time to see who has recurred. I think that that data now goes out to 2 years for some, if not all, of the patients and it is a more reasonable approximation for what the clinician really wants to know. And the same thing can be said for the open-label study in that you treat the patients and you

see what happens.

So the answer to the question about is the outcome measure adequate, it's clearly no for (a) and it may be for (b) but (b) has a lot of other problems in terms of study design that I'll sort of talk about when we try to answer question 3.

DR. DRAKE: Well, I agree with Michael. How could something so straightforward become so complex? Nonetheless, every time we try to look at a study like this, that's exactly what it ends up being. It's very complex.

I would very much like to see something like this available for our patients. I think we need something like this.

Are these measures adequate? I have to say no to part (a). What I'd like to suggest -- and maybe they've got enough data hidden in all this stuff we've heard today because the company has clearly done a lot of work. Maybe the data is in there. Maybe they can tease it out because I think the real utilization of this is going to be in superficial because if not, you're going to have to have a lot more information, in my opinion, about how much to debulk. How thin do you need to make that tumor before you can get the light to where you need to go? Because if people get it out there and they don't debulk it and

they're treating nodulars, I'm not sure they're going to get this good a result because the company spent a lot of time, in my opinion, trying to tell people how to debulk and clinical investigators tend to do what they're told and they do debulk. In real practice, will that happen and how do we advise clinicians on how much to debulk it, I don't know.

So I guess I would say on the surface of what I've seen today, the answer to (a) is no. You might be able to tease some stuff out if they could take a subset of their data set to perhaps make an indication even more narrow. So that's a long answer that doesn't really tell you much, and I'm sorry for the folks at the FDA. I can't give you a better opinion than that.

I'm torn between really wanting something like this and being nervous, as Lloyd pointed out, that the second you turn it loose, unfortunately you're going to have people who don't know the first thing about treating skin cancers out there treating people.

To me we're not here to answer the money or time or any of those questions. We're here to answer is it safe and is it effective. Those are the only two things I think this committee is charged with. I don't care if takes them 6 hours and I don't care what the cost is. The marketplace will sort that out.

What I am very concerned about is the patient. If they go in and get a skin cancer treated and they think it's treated and if it isn't treated, then you could end up with a rodent ulcer. So I don't want that to happen to anybody.

On the other hand, I think many people are over-treated. They spend days in Mohs therapy and what else when they don't actually need it and there are some places where it's just not indicated. And there are places where we don't have good therapy.

To the company, I would recommend highly that they go back and look and see if they have a subset of patients in there that you could frame this around that would be straightforward and a straightforward indication that would help some of our patients.

MS. KNUDSON: Well, I have to say as a consumer I'm totally confused. I am not a biostatistician. I would love to have had something presented in a much more reasonable, orderly, and understandable way, and if I were a patient being asked to consider this new modality as opposed to other modalities, I would probably say no, more because I was totally confused by all of the information I was given than for any other reason.

DR. STERN: Well, I'm sorry I'm so poor at describing the alternative therapies.

DR. TAN: Well, for question (a), I think it's mostly no. I still don't understand why the clinical response -- that's sort of the standard for any cancer drug -- is not used to assess the response rate. I think that is probably the more appropriate measure for the outcome and in conjunction with the time to recurrence. Ideally you want to have probably both of these as endpoints. But we live in real life, but it just would probably take forever, too long to have adequate evidence based on the time to recurrence.

So for the second part of this, it's probably yes. You should have some of this. It's a compromise. So it's just a compromise. I think it is yes to the second one.

DR. RINGEL: In terms of the first study, I think this study is as good as you can do a histologic study. I would have liked to have seen more patients. There were 70 and 80 lesions in either group, which isn't bad. But you can't ethically take a placebo group and tell them to wait 5 years and see what happens. You just can't. So you can't do this study, as far I'm concerned, better than it has been done. I think that asking a patient to wait 6 months is a lot.

Now, could they have done something better than breadloafing? I need to ask our local histopathologist

here. Could they have taken these specimens and done a Mohs processing on them and gotten a better -- is that technically feasible to do Mohs processing on that?

DR. KING: Yes.

DR. RINGEL: So that would be certainly one way to make the study better. So at least you could have looked at all the margins. It would have certainly helped.

But the problem with the histopath studies is that if the margin is negative, it can still recur, and if the margin is positive, it may not recur. So you're always limited. As much as it's nice to say, oh, well, I have a test, I can see if a cancer is there because I have the test, if the test isn't 100 percent sensitive and specific, it may not be such a great test.

What I'd like as a clinician frankly is the other study, the long-term study. I want to know following that patient for 5 years, is it recurring. Frankly, if there are a couple cells left there histologically but they're not recurring clinically and they're just going to sit there for another 10 years and the person is going to die of something else, frankly, I don't care. I want to know how did that patient do in 5 years. I would like to see two of those studies carried out for a long period of time. Yes, I'd like to see the other histologic study, but what I really care about are long-term results.

DR. STERN: As we go to the next question, I want to ask, so we won't get into semantics here, the agency for a couple of clarifications on this question. The question is, has adequate evidence been presented to support a primary indication for the treatment of basal cell carcinoma for this product? I'd like you to define primary and say whether you're asking us here about nodular only or nodular and superficial before we go around. So could you help me with that?

DR. WILKIN: Well, of course, we sometimes like to modify questions a bit after we've heard discussion. So I take your point that this could be subdivided into different sort of niche indications.

What we originally meant by primary was first-line therapy.

DR. STERN: That's fine. Just so we know what you meant by that.

And how about the basal cell carcinoma or nodular basal cell carcinoma?

DR. WILKIN: Sure. I think that it can be overall basal cell carcinoma, if the committee wants to consider that. We looked at nodular primarily. There are some data, of course, for superficial. I think we spoke to the recurrence data set. So I suppose it could be either nodular or superficial or nodular and superficial that

would be the options for the committee.

DR. STERN: With the agency's permission, which I think might speed things along, this is a yes/no and I would ask people, first of all, to say do they believe that there's adequate efficacy information for this as a first-line therapy for basal cell carcinoma. If the answer to that is yes, then they should specify whether it's, based on the evidence, nodular, nodular and superficial, or basal cell carcinoma not otherwise supervised that they believe the efficacy information supports. Is that acceptable to the agency in terms of how to ask this question? Because I'm afraid we're going to get into this, oh, I'd love it for superficials, but I wouldn't use it for nodulars.

So the question is first-line therapy for basal cell. I guess, if so, do you believe the evidence restricts it to any subtypes. Maybe that's an easier way of saying qualify it based on the evidence.

Yes.

DR. BULL: I would remind the committee once again that you have to make your deliberations based on the data you have on hand. There's a question that comes later that does address whether or not further studies or if you want to ask for some subgroup analyses, but there's opportunity to ask for more exploration of where you see the need or potential use of the product based on what

you've reviewed.

DR. STERN: So data-driven, not what we'd like, but what we see.

Jimmy.

DR. SCHMIDT: Yes for nodular BCC and superficial BCC, and I would exclude morpheaform, the other types.

DR. TEN HAVE: Being a biostatistician, it's probably not appropriate for me to comment on this, but I'm going to try anyway.

Just to clarify in my mind what the picture is, again, the distinction between superficial and nodular has an impact on what studies we consider. I'm going back to the point of conversation we had earlier. It seems to me, again, that the cryotherapy versus MAL trial was the superficial BCC trial. Right? And that's key in my mind. That's where MAL did well in the long-term recurrent rate department, and I'm going to say because of that I think superficial is where it should be targeted.

DR. STERN: So if I understand you, it was yes, superficial only.

DR. TEN HAVE: Right.

DR. STERN: Thank you.

DR. RAIMER: I'm fudging a bit too. For me it is yes, but it's only for those lesions that are unsuitable

for other available therapies.

DR. STERN: I do not think that I could support this as a first-line therapy based on the evaluable evidence. So I don't have to specify what type.

DR. SAWADA: I too would not consider this as first-line therapy. I'd have to say no.

DR. KATZ: No.

DR. KING: As a primary therapy, I have to go with no. I think that the sponsor has already eliminated sclerosing and infiltrative and so forth. So that's not there. So the answer would be no if you mean primary therapy.

DR. BIGBY: I would also say no, and I'd just like to remind the advisory panel that what we're looking at is two randomized, placebo-controlled trials with basically 30 people in control and active arms in two separate studies and a difference between placebo that has a confidence interval that at the lower end was 18 percent in one study and 24 percent in the other.

It never ceases to amaze me how limited the amount of efficacy evidence that's actually presented is. I think as long as we sort of keep advising to approve treatments where this is the level of evidence we get, we'll always get this level of evidence.

DR. DRAKE: As a primary, I'd have to say no.

A subset, I have a different opinion, but I'm going to leave. I apologize. I told you I had to leave early. I might have a different opinion on a subset, but as a primary I'd have to say no right now.

MS. KNUDSON: I also will say no.

DR. TAN: I will say no, not as first-line because we really need to reconcile the 6 months' efficacy with the recurrence rate.

DR. RINGEL: No.

DR. STERN: May I ask the agency? Is question 4 still relevant, given what we've said in response to question 3? There were 3 yeses and 9 noes in response to question 3.

DR. WILKIN: I think for comment we may eventually have more studies, and to keep from coming back to the committee, what we'd, I think, like to hear is, is there something that you would suggest would go in the indication section sort of to frame, just some general kinds of comments?

DR. STERN: I don't know how we can do it with the data we have.

DR. BIGBY: Wait. I really don't understand this question. I don't understand what it is that you're asking.

DR. WILKIN: Okay, fair enough. What we are

asking actually has some basis in what we've heard around the table today. You spent a lot of time talking about standard of care and what you believed to be the rates of success with other modalities. Basically the question is those other modalities -- is there a role for that information in labeling should this product eventually be approved for primary all basal cell carcinomas or any particular subset. So it's sort of hypothetical but in that construct, would you see a role for that information about those other modalities crafted into labeling? That's the basis.

DR. STERN: With that context, this surprises me because every new label I see basically summarizes the results of the studies that were accepted in going into the label, and clearly whether there's an active comparator or a placebo comparator, those data are presented as part of at least all the package inserts I see coming rolling out. Of course, the information is useful and our problem is that there's not enough information yet about this drug relative to comparator.

DR. BULL: Not being a dermatologist here, but in the discussions I've participated in with the division, as we were trying to craft the questions, I think there was a concern that we bring to you all as our experts who are in clinical practice as to contextually where this therapy

fits in or if you have a therapy that may be viewed at least by the existing body of data as potentially less efficacious than the "standard of care." I think there has been comment made that that body of data is probably not the best, but if there was any comment the committee might provide as to how that might be given. We do have some studies that did compare to surgical treatment.

DR. KATZ: Related to that, when you say the data is not adequate, nothing is perfect.

DR. BULL: Right.

DR. KATZ: But the fact is that in the literature repeatedly we see the same numbers. As was pointed out, people don't report sometimes if they have poor results, but generally speaking, what is in the literature is fairly close and it also is consistent with what many of us see -- I didn't poll everybody of my colleagues -- in the office. So I would disagree that, oh, the data we have on recurrences, we can't believe anything about it. That impression should not persist. We have a pretty good idea of how frequent recurrences are.

DR. STERN: Other comments on 4? Michael?

DR. BIGBY: So if I understand this correctly, what I would say is that the best information that one could convey to our colleagues would be the results of head-to-head trials in terms of how it compared to placebo,

cryotherapy, and surgery. That would be the advice that I would give people because based on available data, that's the best data that there is.

DR. STERN: Question 5, safety. Please discuss the adequacy of the safety assessment, including the contact sensitization assessment and the adequacy of data on recurrence rates. I would say that we've answered the issues of the adequacy of data on recurrence rates ad nauseam and would prefer to just address the issue of contact sensitization. I've forgotten where I was last time going around the room, but I think I'll start with Eileen.

DR. RINGEL: I think they're almost there but not quite. I'd like to see some longer-term studies done with patch testing in the way that people are going to use this. For example, it doesn't seem that after four treatments people have a significant rate of contact sensitization, at least clinically, but people will theoretically keep on getting basal cell carcinomas for years to come and they may potentially be exposed over and over and over and over again. So it seems to me it might be relatively easy to do a study of the 3-hour application, wait a day, a 3-hour application, wait. In other words, see how many 3-hour applications you can get until you do get contact sensitization, and that might be useful

information, more in the way that it will be used clinically.

And the second issue is I would want to make sure that whatever gloves physicians are using, that this agent cannot penetrate it. So I'd like to make sure that this is good for latex gloves, vinyl gloves, the rest.

DR. TAN: Yes, I would defer this to our physician scientists because there was debate about whether this is relevant.

MS. KNUDSON: My concern was the sensitization and irritancy that were in the normal subjects. 52 percent of them had reactions with long exposures. So I second what Eileen said in terms of the health care provider.

DR. BIGBY: I'm actually satisfied with the sponsor's assessment of the risk to patients. I do share the concern about making sure that health care workers protect themselves from this, especially if they are going to be doing this frequently.

DR. KING: Having wrestled with the FDA over orphan drug indications for diphencyprone for about two-and-a-half years, it becomes one of the issues of is the chemical available in the environment so there's going to be cross-sensitization. I recognize the argument that benzoyl peroxide and a number of agents like preservatives are available, and they're approved for over-the-counter.

I think that's a little bit different from saying you're going to sensitize somebody to an endogenous ALA which all cells contain in the mitochondria, et cetera.

Actually I was hoping they would turn out to be that the MAL would be a unique chemical and we could use it for alopecia areata as an FDA-approved drug.

Having said that, 2 percent of a big number is still a big number, and I am concerned. I applaud their efforts. I'd just like to know a little bit more about that. So you can't get a drug approved, as I know, over the counter if you have a 2 percent incidence of sensitization for fragrances, et cetera. So I'd like to see a little more data about that.

DR. KATZ: Yes, I think the safety assessment has been adequate. It is somewhat worrisome on contact sensitization of that percentage of people, but as was properly pointed out, if you're treating some skin cancers and somebody gets an allergic contact dermatitis, then you treat it. It's really no big deal. We treat contact dermatitis in the office during the summer multiple times a day, and that person would not be appropriate for further treatment with that. So that doesn't bother me. What bothers me is the recurrence rates and the ineffectiveness relatively of the drug. But I think adequate safety assessments were done, and I think appropriate comments

were made on it not being a terribly worrisome thing if the patients developed a contact dermatitis.

DR. SAWADA: Again, I noted the high rate of contact sensitization with the patients. Again, that's good and well. I think what the company provided was good information.

But again, I echo Eileen's concern if I were the one who became sensitized to this in giving it. I worry about my staff and myself. So I'd like to see a little bit more data on that aspect and what kind of protective measures we need to take to avoid sensitization.

DR. STERN: I have no comments on sensitization.

One thing that I did not see in the safety data -- or perhaps I missed it -- is the persistence of photosensitivity, since there is lots of red light when you go out and a lot of these lesions are in exposed areas. It's visible light, and what about inadvertent exposure and sensitization to other sites? Have you done in normal skin, in fact, MPDs to look at if you apply this cream and you irradiate it on normal tissue, whether or not you get what the MPD is, how long an equivalent of sunlight? So I think those data, if they exist, certainly need to be shared. When you put ALA on normal skin, you get photosensitization.

I understand that you've shown pictures that you don't see fluorescence on mice where it's not applied, but I'd like to see some actual human data with application of the agent to normal skin. But that may be there. And then if you've got it covered, the agency will pay attention to it.

DR. KATZ: I also wanted to add the emphasis. We should put a lot of priority on the clinicians not seeing problems with the drug. So we may get sensitization with the sensitivity studies, but when so many patients have been treated and they just haven't seen contact dermatitis, that would be a very obvious thing. So we must put a lot of credence on that for this aspect of the problem.

DR. RAIMER: Yes, I agree with others. I don't really have things to add. But I do think the possibility of the cross-sensitization with the ALA needs to be monitored continuously.

DR. SCHMIDT: I love to see a contact dermatitis to 5-FU and some of these other things. I think you get your best results. So actually, to kind of spice the pot a little bit with a contact dermatitis is good. So I go along with that they did show the adequacy of the recurrence rate and the contact sensitivity assessment.

DR. STERN: Now we go on to question 6, which

is I believe a voting question. This question is, based on the safety and efficacy data, does the committee find a favorable risk versus benefit balance to support approval of this product?

DR. SCHMIDT: Why do I always get to be the first?

(Laughter.)

DR. SCHMIDT: This is a tough one. No, no. I'm not trying to weasel out.

I'd say yes.

DR. TEN HAVE: Do I get to vote?

(Laughter.)

DR. TEN HAVE: Given my past comments, I would vote yes for the superficial indication.

DR. RAIMER: How are we voting? Are we just voting in general? We're not voting for specific types of tumor, are we? We're just voting on the data that we have, do we think it's adequate.

As much as I would like to have it for superficial, at the moment I'm not sure that the data is adequate. I'm going to vote no.

DR. STERN: No.

DR. SAWADA: No.

DR. KATZ: No.

DR. KING: No.

DR. BIGBY: No.

MS. KNUDSON: No.

DR. TAN: No.

DR. RINGEL: No.

DR. STERN: The next question is additional studies. Please discuss whether any additional studies may be needed and whether these studies might be conducted after approval, which is hard after the prior question to ask, although I suppose sometime in the far future. Perhaps we could put it, please discuss what you might think would be useful pre-approval and post-approval studies, should the agent eventually be approved. How about that for a question?

I think we've already made lots of suggestions, so it would be additional things that either you as an individual have not said or have not heard other people say. With that, I would say I don't have anything to say that I haven't. I can't think of additional things that someone hasn't raised as additional studies, ways to design them, et cetera.

DR. SCHMIDT: I agree with you.

DR. TEN HAVE: Same here.

DR. KATZ: Well, the drug has shown to be more effective than placebo, and I would think that if the sponsor could show, so to speak, a niche where we would

say, oh, yes, that's a place that we could use in that patient as advantageous over what we have available, I think that would be very interesting.

DR. KING: I think that I have a two-part answer. One, I'd like to see larger numbers simply because for a million-plus people, that's not very many numbers. I guess in the real world it's hard to do these. They're expensive and time-consuming.

But I'd like to see something that when they define the type of basal cell, they put in the category of nodular by itself or solid with or without infiltrative features and so forth and then give the depth. We know that's an important part of the melanoma. And I'd also like ulcerations. I'd like a more precise description as a dermatopathologist of what you start with. At some point you would have clinical and the pathology or histopathology of the lesion, and then for those that fail, I'd like to see a histological evaluation to correlate with the clinical. That would also include at the time of applying it. Since we're saying that MAL is tumor-specific, just shine the black light on it or confocal fluorescent microscopy and determine if why it's persisting is, instead of just having a nodular, you have then the heterogeneous tumor which has biologically aggressive features such as the sclerosing or morpheaform, et cetera.

That may explain in my experience why things come back because oftentimes you'll diagnose, based on a small section, a nodular tumor, and then when it recurs, it comes back to you. You have to look back and say that's not a nodular. On an excision or the recurrence, you have a totally different biological appearance, I mean, regression, based on it's no longer just a simple nodular.

So I'd go for clinical histology and the repeat and then the porphyrin specificity.

DR. BIGBY: I just think that the problem study for this application really is the placebo-controlled trial and the fact that they had such high cure rates in the placebo arm. I think it's fairly obvious what needs to be done in terms of a study to explain that and to sort of ferret out what in this therapy is the effective modality.

MS. KNUDSON: I'll echo all that was said.

DR. TAN: Yes, probably some more studies need to be conducted, by first carefully looking at the current data and I think a cleverly designed study, especially taking into consideration keeping the response rate up, but at the same time keep the recurrence rate down. I think that's the key. Those two things have to be there.

DR. RINGEL: I think that they need to design a study for the patient population in which it will be used, and from what I've heard today, mostly that includes

lesions of large diameter on the trunk and extremities in patients who are not surgical candidates because of bleeding, diathesis, or whatever.

I would not, just as an additional point, use this on the face. I think that the failure rate that I heard of 48 percent is so high, I think I would never use this on the face. They can do Mohs surgery. I just don't see the point of it. I just wouldn't do it.

The other thing is I think I would make very clear that this is something that's used in patients who are not candidates for surgery. What I worry about is what many people have said: this is too easy to use. Anybody can get their hands on this and do it. It doesn't sound like you need a whole lot of training. It's going to cost some money, probably buying, leasing this light. Once you purchase it, you're going to want to get your money's worth out of it, and you'll be tempted to use it on perhaps more patients than it should be. So I think we need to make very clear that this is for patients who cannot, for one reason or another, be treated by surgery, for large lesions, for bleeding lesions, not for lesions on the face.

DR. STERN: The final question that the agency has put to the committee is, as I understand it, a generic one. For future development of drug products for basal cell cancer -- in other words, not limited to this

sponsor's product -- please discuss which measures should be the primary efficacy measures, clinical evaluation and/or histologic clearing and the time points as well as recurrence rates and appropriate time points.

Again, I would ask the committee to add things that they don't believe have been covered because I think we've spent a large amount of time addressing these issues as it applies to this, but in a way that has, in fact, been very broad-ranging that is generally applicable to what we'd want to see for a product for basal cell. So at least I have no comments to make beyond those that have been made by the committee already.

DR. SCHMIDT: I agree, but I think just in way of review, I think that when they do the histology, to do the Mohs where you slice it, where you can see the sides and the base, and then to extend these studies out to try to get the recurrence rates for like 2 to 5 years because I know these are going to come up.

DR. TEN HAVE: This is probably a more general question that we actually asked earlier about non-inferiority trials regarding the threshold of 15 percent. You asked that question before lunch.

DR. STERN: Yes, thank you. I'm sorry. I guess to me that in powering studies, I do not consider an incidence/rate ratio of 4 with an underlying assumption of

a 5 percent failure rate in the comparator group to show non-inferiority to be adequate. Powering a study to exclude an increased risk of 4-fold higher an incidence, assuming 5 percent in the compared-to therapy, is too high a margin. I would have to say that if I were powering studies, if the assumed recurrence rate is as high as 5 percent in the treatment to which the innovator is being compared, I would want the odds of recurrence at 2 years to be no more than double. To say to a patient, well, as far as we know, we're pretty sure it's not going to be more than four times as much, that's not enough powering in a non-inferiority trial. So to me, when you're talking about a doubling of risk assuming a relatively low risk for the baseline comparison of, say, 5 percent, that's clinically acceptable because then there are tradeoffs. When you're talking I can only exclude it being four times more likely that you're going to have a recurrence, I don't think that's adequate powering. Thank you.

DR. RAIMER: I think it's very unusual that you see clinical recurrence of a lesion at 6 months after it's been treated. I would suspect that histologically there are very few cells there even if it's going to recur. So I think it would be hard to demonstrate most of the time histologically.

I agree with Eileen that you can't ask somebody

to undergo a placebo treatment and have a long-term study, and you can't expect somebody to want their lesion excised 2 years after it's been removed, especially if it clinically looks good.

So I think maybe more clinical studies that are maybe not even placebo-controlled, more long-term clinical studies using this entity, looking for clinical recurrence and then biopsying if there's anything suspicious at all need to be carried out. I'd like to see them at least 2 to 5 years.

DR. SAWADA: And I just have to agree with Dr. Raimer. I would want to see these studies further out.

DR. KATZ: I have nothing to add.

DR. KING: I've said all I really want to say except I'd like for this to be approved in principle and just power to study more and have more patients involved and try to find the heterogeneity.

MS. KNUDSON: I have nothing to add.

DR. TAN: Again, I said before that I don't understand why clinical response is not used. So, therefore, I would like to have the clinical response to be used. For anticancer drugs, they use this so-called objective response which is a combination of the histological response and the clinical observation. So they have several pages of this to define how they derive

that. I think that will be very helpful to design future trials.

Of course, any trial like this probably, given the high success rate of the current therapy like the surgery, you always need to consider other parameters. In this particular example we discussed today, it was the recurrence rate. For some other products, maybe some other parameter needs to be considered because in terms of response rate, you probably cannot really beat the surgery.

DR. RINGEL: I think that the primary efficacy studies should be unfortunately the one that's not controlled but long-term like 303 was, but carried out at least 3 years. According to the article that you gave us by Daniel Rowe, 3 years has 66 percent of the recurrences, which is over half. You can make mathematical calculations at that point. So I'd say at least 3 years. 5 would be preferable, but I think 3 should be enough.

And then because those can't be placebo-controlled studies, I think that it would be nice to have studies like 307 and 308, and I think we should have both available but the primary efficacy studies should be the long-term ones, the clinical ones.

DR. STERN: Does the sponsor have any questions or final comments, questions for the committee before we close?

DR. MORRIS: No.

DR. POSNER: Can I just make one comment?

DR. STERN: Sure.

DR. POSNER: I would just like to point out that the cryotherapy results are fact. They show no difference. Whichever way you look at them, they show no difference between MAL-PDT and cryotherapy. That's fact. That's not opinion. Really the difference between publication bias and a randomized, multi-center clinical trial in this fashion are really so different that we would stand by those results. We do feel that they should be taken into account in the overall assessment of efficacy.

DR. STERN: Thank you.

And does the FDA have any final comments, questions, criticisms?

DR. WILKIN: I don't think any final questions, but certainly we're grateful for not just going through the questions and giving us all the abundant information there, but as you probably know, we go back over the transcripts for the entire session, and you had quite a bit of discussion this morning and then you started again at 1:00. So we have a lot ahead of us to pore over and we are very much appreciative of the thought that you've given this. Thank you.

DR. STERN: Therefore, the meeting is

adjourned. Thank you all very much, sponsor, FDA, and participants. Thank you.

(Whereupon, at 3:48 p.m., the committee was adjourned.)