FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

8:33 a.m

Thursday, June 26, 2003

Marriott Washingtonian Center
9751 Washingtonian Boulevard
Gaithersburg, Maryland

ATTENDEES

COMMITTEE MEMBERS:

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ATTENDEES (Continued)

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS: (Voting)

OTIS BRAWLEY, M.D.
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Birmingham, Alabama

DAVID KELSEN, M.D.
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SPECIAL GOVERNMENT EMPLOYEES: (Voting)

JAMES GILLETT, PH.D., Patient Representative
Department of Natural Resources
Ithaca, New York

ALLEN MANGEL, M.D., PH.D.
Research Triangle Institute
Research Triangle Park, North Carolina

ACTING INDUSTRY REPRESENTATIVE: (Non-voting)

GEORGE S. GOLDSTEIN, M.D.
White Plains, New York

FOOD AND DRUG ADMINISTRATION STAFF:

MILTON FAN, PH.D.
HUGO GALLO-TORRES, M.D.
FLORENCE HOUN, M.D., M.P.H.
ROBERT JUSTICE, M.D.
EDVARDAS KAMINSKAS, M.D.

ATTENDEES (Continued)

AXCAN SCANDIPHARM, INC. REPRESENTATIVES:

MARY P. BRONNER, M.D.
PATRICK COLIN, B.PHARM., PH.D.
ALLAN DONNER, PH.D.
FRANCOIS MARTIN, M.D.
BERGEIN F. OVERHOLT, M.D.
KENNETH K. WANG, M.D.

C O N T E N T S

NDA 21-525, Photofrin (porfirmer sodium),
Axcan Scandipharm, Inc.
Photodynamic therapy with Photofrin is indicated for the ablation of high-grade dysplasia in Barrett's esophagus among patients who refuse esophagectomy and who are in overall good health.

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C O N T E N T S (Continued)

P R O C E E D I N G S

(8:33 a.m.)

DR. WOLFE: Good morning everyone. It is a little past 8:30. I think we'll get started and try to stay on schedule as much as possible. I'd like to welcome you all to today's advisory meeting for the Committee on Gastrointestinal Drugs.

I'm Michael Wolfe. I'm a professor of medicine at Boston University School of Medicine, and I'm the Chair of the Advisory Committee for Gastrointestinal Drugs for the FDA. Unless there's some kind of emergency in the next four days, it's also my last meeting as chair, and it has been an enjoyable experience.

Before Mr. Perez reads the meeting statement, I'd like everyone to introduce themselves at this table. George?

DR. GOLDSTEIN: George Goldstein, Vice President, Regulatory Affairs for Mankind Corporation, acting industry representative to the panel.

DR. MANGEL: Allen Mangel, Research Triangle Institute.

DR. KELSEN: David Kelsen, medical oncology, Sloan-Kettering, New York.

MS. COHEN: Susan Cohen, consumer member.

DR. GILLETT: Jim Gillett, Cornell University

and Esophageal Cancer Awareness Association, President.

MR. PEREZ: Tom Perez, Executive Secretary to this meeting.

DR. LEVINE: Bob Levine, Upstate Medical Center, State University of New York, and a member of the committee.

DR. BRAWLEY: Otis Brawley. I'm a medical oncologist and epidemiologist at Emory University in Atlanta.

DR. SHIH: Weichung Joe Shih, University of Medicine and Dentistry of New Jersey. I'm a biostatistician.

DR. CARPENTER: John Carpenter. I'm a medical oncologist from the University of Alabama at Birmingham.

DR. CAMILLERI: Michael Camilleri, Mayo Clinic, Rochester, Minnesota, a member of the GI Advisory Committee.

DR. KAMINSKAS: Edward Kaminskas. I'm a medical reviewer in the Division of Gastrointestinal and Coagulation Drug Products, FDA.

DR. GALLO-TORRES: Hugo Gallo-Torres, a medical team leader in the Division of Gastrointestinal and Coagulation Drug Products, FDA.

DR. JUSTICE: Robert Justice, Director of the Division of Gastrointestinal and Coagulation Drug Products.

DR. HOUN: Florence Houn, Office Director for Drug Evaluation III in FDA.

DR. WOLFE: Thank you. After you speak, although it's not absolutely necessary, if you can turn your microphone off, it does help. There may be occasional feedback otherwise.

Mr. Perez will now read the meeting statement.

MR. PEREZ: Thank you and good morning.

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

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

We would, however, like to note for the record that Dr. George Goldstein is participating in this meeting as a non-voting acting industry representative.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the

participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

Thank you.

DR. WOLFE: Thank you, Tom.

Dr. Justice will now offer some opening comments.

DR. JUSTICE: Before I talk briefly about the current application, I'd just like to comment that we have two members who are rotating off the committee today, Dr. Wolfe and Dr. Richter. On behalf of the division and the office, I'd like to thank you for your time and effort and expert advice that you've provided over the last few years, and we very much appreciate it.

Again, I'd like to thank the committee and consultants for participating in today's meeting. Photodynamic therapy with Photofrin was originally approved for the palliation of patients with completely obstructing esophageal cancer or partially obstructing esophageal cancer which cannot be satisfactorily treated with laser therapy.

It was subsequently approved for the reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small cell lung cancer and for the treatment of micro-invasive endobronchial non-small cell lung cancer in patients for whom surgery and radiotherapy are not indicated.

Today's application seeks approval for the ablation of high-grade dysplasia in Barrett's esophagus among patients who refuse esophagectomy and who are in overall good health.

The primary study supporting the application is PHO BAR 01, a randomized, multicenter, open-label trial of Photofrin photodynamic therapy plus omeprazole versus omeprazole alone. There are also two supportive single-center trials, one of which randomized the two light doses and the other which randomized to steroids or not to assess the effect on strictures. Minimum patient follow-up in these trials was 12 months.

The major issues that we would like the committee to consider are, first, the high rate of failure to confirm the diagnosis of high-grade dysplasia by the central reference laboratory. What implications does this have for the use of photodynamic therapy with Photofrin outside of a clinical trial?

Second, do the data from PHO BAR 01 demonstrate

that photodynamic therapy with Photofrin is effective in completely ablating high-grade dysplasia in Barrett's esophagus?

Third, is a 2-year follow-up period adequate to demonstrate cancer risk reduction in patients with high-grade dysplasia in Barrett's esophagus following photodynamic therapy with Photofrin? If not, will 5 years of follow-up be adequate?

Finally, is the safety profile of photodynamic therapy with Photofrin in this patient population acceptable?

We look forward to receiving the committee's advice on these issues. With that, I'll turn it back over to the chair.

DR. WOLFE: Thank you, Dr. Justice.

The sponsor Axcan will now begin their presentation, and I hope I pronounce this right. Dr. Francois Martin.

DR. MARTIN: Don't worry. I won't give my presentation in French.

(Laughter.)

DR. MARTIN: Good morning all. Mr. Chairman, members of the GI Advisory Committee, members of the Oncology Advisory Committee, special government employees, my colleagues, on behalf of Axcan Pharma, I want to thank

the division for giving us the opportunity to present to the advisory committee the scientific evidence to support our proposal for a novel treatment modality for the per-endoscopic ablation of a premalignant condition, the high-grade dysplasia in Barrett's esophagus.

Photodynamic therapy, PDT, requires the combined use of a pharmacological agent and a light delivery system. Photofrin, porfirmer sodium, is the drug agent. It is a cell photosensitizer which is administered parenterally. The light delivery system is made of interrelated devices used to deliver activating laser light to target tissue. Balloon catheters, fiber optic diffusers, and laser light emitters are used.

Photofrin, porfirmer sodium, is the cell photosensitizer that needs to be administered in a single, slow intravenous injection over a 3- to 5-minute period at a 2 milligram per kilogram body weight.

Centering balloon catheters with opaque tips made of silver inside lining, specially made to increase and contain light reflection, are used. These balloon catheters of different window sizes of 3, 5, or 7 centimeters are made to hold the fiber optic light diffusers, also of different window size of 5, 7, and 9 centimeters, and are positioned inside the balloon for stability and uniformity of light diffusion.

To illuminate mucosal nodules as a pretreatment procedure or complete illumination of isolated BE segments, shorter cylindrical diffuser or bare tip fibers are currently used for direct application to the mucosa.

The first systems used for PDT were Coherent laser systems and Laserscope. Coherent is the big system here, and Laserscope is here. Coherent is an argon dye laser, whilst the Laserscope engineered a dye laser module that can be connected to the KTP Yag laser.

The first generation technology has several limitations. They are large in size, require special electrical connection, and water cooling. More recently the company Diomed has engineered a new diode laser which is compact and portable, air-cooled, and there is a pre-program that is user-friendly, makes the use of a touch-on screen to establish the time and energy delivery parameter individualized to each patient.

We have presented equivalence for this Diomed laser with the other two lasers in our submission, although no patients in our study were treated with this laser apparatus.

The dysplastic cell destruction created by PDT is mediated largely by the generation of singlet oxygen. Intracellular Photofrin absorbs light and transfers this energy to molecular oxygen to create singlet oxygen.

Porphyrins normally bind to low-density lipoprotein in the blood serum. It has been proposed that low-density lipoprotein receptors play an integral role in the porphyrin localization in and on tumor cells. So this propagation of superoxidative reaction bringing in the oxygen triplet causes ischemic necrosis in the cell and leads to cell destruction.

Here's an overview of the PDT process. Photodynamic therapy begins with the IV administration of a photosensitizer, and this drug makes patients sensitive to sunlight for approximately 30 to 90 days. Their greatest photosensitivity is during the first 2 weeks after injection. Patients need to wear protective clothing that shields their skin from all light exposure.

48 hours after the drug is injected, photo illumination is performed. At that time, the patients are given supplemental oxygen via a nasal catheter. Oxygen is a key component of therapy and it is required to generate singlet oxygen.

The damage produced by photodynamic therapy is not visible immediately after the first course of treatment. Therefore, not uncommonly patients have to return 38 to 48 hours after the first course for inspection of their esophagus.

A second laser light application may be given

to a previously treated segment in which there was insufficient mucosal response or skip area. Patients with remaining persistent dysplasia, persistent Barrett's, or untreated segments should be treated for a second PDT course no earlier than 90 days later.

The PDT process. The laser light is applied to the esophageal mucosa. An argon pump dye laser or diode laser is tuned to a wavelength of 630 nanometers and that delivers light endoscopically through the window centered esophageal balloon catheter system. Power density is typically between 200 and 270 milliwatt per centimeter of diffusion, providing energy density of approximately 130 joules per centimeter to tissue. The advantage conferred by the centering balloon is the uniformity of energy delivery to the target area.

Dr. Justice presented the already approved indications for PDT and Photofrin in several conditions. I just had the dates of approval for esophageal cancer in its palliative treatment component. It's been approved in January 1998 for non-small cell cancer, the curative aspect of it, and non-small cell cancer for palliation of obstructive bronchial cancer.

Barrett's esophagus is a morphological condition with a serious potential for malignant transformation. The sequential progression up to high-

grade dysplasia in a small proportion of patients with GERD condition is considered, nonetheless, a very serious premalignant condition since, when the condition has progressed to HGD, a 30 percent increased risk of progressing to invasive adenocarcinoma is present. Consequently, this evolution of Barrett's esophagus to HGD requires a radical therapeutic intervention, either a surgical resection or an alternative form of ablative therapy.

In our submission, we have this proposed indication: ablation of high-grade dysplasia in Barrett's esophagus among patients who refuse esophagectomy and who are in overall good health. We believe that we have generated strong clinical evidence that Photofrin PDT is an efficacious and safe, nonsurgical alternative to esophagectomy for patients who have progressed to HGD. We have proposed a very conservative indication for this novel therapy in our submission, and this is in complete respect of the current practice. But considering the results of our pivotal trial, especially the absolute risk reduction in the progression to cancer, it suggests that we ask this committee here to look into the possibility of perhaps broadening this indication to a more generalized, less restrictive population.

Concerning this submission, here is the

relevant regulatory history. There was an end of phase II meeting which was held in 1997 where the essentials of the protocol considered as our pivotal phase III trial, called here PHO BAR 01, were agreed upon, and the acceptation by the division to include two non-pivotal investigator-sponsored studies that needed to be reanalyzed in accordance to the endpoints for efficacy and safety of the pivotal trial. At that meeting, esophagectomy was ruled out as a comparative therapy.

An orphan drug designation was obtained from the division in October 2001. We also received, much to our satisfaction, supporting our continuing effort, this acceptation for a priority review in July 2002, and the reception from the Gastrointestinal Division of an approvable letter for our NDA was also a great stimulation to maintain our continued effort to make this novel therapy approved as a new therapeutic option for patients suffering from this serious premalignant condition.

The current status for this novel therapy in other countries is as follows. It was approved in Canada March 14, 2003, and it is under review in Europe and the decision is expected November 2003.

So we will present what our NDA application is composed of, and it's based on a large multicenter, partially blinded pivotal trial and two supportive studies,

with a total of 399 patients studied, of which 219 had high-grade dysplasia and had received the PDT Photofrin therapy.

The endpoints that were studied were for the primary endpoint, the complete ablation of high-grade dysplasia. You'll hear about the definition of CR1, CR2, CR3 for your understanding.

Secondary endpoints were quality of complete response, duration of complete response, time to progression to cancer, time to treatment failure, as well as survival time.

I'm not anticipating what I will say after the presentation, but I think we are proud to put forward some conclusions concerning the efficacy of our trial, and I think we can fairly say, as you will see from the upcoming presentation, that Photofrin PDT plus omeprazole is significantly more effective than omeprazole alone in the ablation of HGD in Barrett's esophagus. Concerning safety, this treatment modality is an acceptable treatment option for ablative therapy in HGD.

We are also ready for discussing issues that you might see pertinent here, namely, concerning screening failures -- Dr. Justice has alluded to that already -- the length of evaluation time, the comparative therapy, intervening therapy for patients who have progressed to

more severe conditions, and patient selection concerning the label or the proposed indication.

I've gone through the first portion of our agenda. I will now have colleagues who will present on the management of HGD in Barrett's esophagus, Dr. Kenneth Wang, who is Associate Professor, Director of Barrett's esophagus Unit at Mayo Clinic, Rochester, Minnesota. Dr. Bergein Overholt, Medical Director, Laser Center, Thompson Cancer Survival Center in Knoxville will present the clinical data, mainly the pivotal study. Dr. Mary P. Bronner, Director of GI and Hepatic Pathology, Cleveland Clinic Foundation, will address histopathological issues related to diagnosis and follow-up of patients with high-grade dysplasia. And I'll come back later on to conclude.

Thank you for your attention. Is this agenda acceptable to the chairman? Thank you.

Yes. I'm sorry. I want to identify the consultants who are here with us today. Mary P. Bronner will be a speaker later on. Allan Donner, with 2 L's, is Professor and Chairman, Department of Epidemiology and Biostatistics, University of Western Ontario, Canada. Dr. Overholt and Dr. Wang.

DR. WANG: Hi, ladies and gentlemen. Thank you very much for giving me the opportunity to talk to you today about the management of Barrett's esophagus with

high-grade dysplasia.

My first slide illustrates why there is a problem with Barrett's esophagus. Basically there have been seven studies that have come out that have said that there's an increased incidence in esophageal adenocarcinoma in western countries, four of these from the United States, three of these from Europe, all concluding the same thing, that there's been a geometric increase in the incidence of esophageal adenocarcinoma. This highlights the crux of the problem. We know we're kind sitting on the peak of an epidemic and we think that the cause of this is this lesion, Barrett's esophagus.

As shown on the panel on your left, this is an endoscopic view of the esophagus. The proximal portion, where the arrow is, is the normal squamous, whitish epithelium. Distal to this is this reddish columnar replacement of this epithelium by what is termed specialized intestinal metaplasia, or Barrett's mucosa. This is defined microscopically as columnar epithelium containing goblet cells, and these are necessary features, both the visible segment and the histological features, for diagnosis of Barrett's esophagus.

Now, the epidemiology of Barrett's esophagus is also well known. Basically it's associated with chronic gastroesophageal reflux disease which 7 percent of the U.S.

population is known to have daily. 10 percent of chronic heartburn sufferers, patients with GERD, are thought to have Barrett's esophagus. With this risk of esophageal cancer in Barrett's esophagus, we have come up with statistics such as 30 to 60 times increased risk in the general population and up to 2 percent increased risk of cancer developing in patients with Barrett's esophagus.

Now, the pathogenesis of this condition is thought to occur obviously starting with gastroesophageal reflux. Various constituents of the refluxate such as acid, biosalts, and pancreatic enzymes may play a role in causing injury to the epithelium. This injury produces esophagitis or inflammation of the mucosa which can then undergo two rounds, either restitution back to the normal squamous epithelium or metaplasia and production of Barrett's esophagus, which is thought to be a more acid-resistant epithelium which is why it occurs.

Now, this slide illustrates the progression to cancer from Barrett's esophagus. On the left is actually the normal squamous epithelium. Then you progress on to metaplasia, or Barrett's esophagus. From this point on, it is endoscopically indistinguishable, these various stages. Whether you have low-grade dysplasia, high-grade dysplasia, we really can't tell in endoscopy. It still looks fairly flat and fairly reddish in nature. However, on random

biopsies, which are currently advised to survey these patients, you see features such as loss of nuclear polarity and even invasion when we get down to the region of cancer.

The progression of high-grade dysplasia in Barrett's esophagus to cancer has been studied. Three major studies have been placed out there, one from our institution and one from the group at the University of Washington with Brian Reid. Both indicate that there's a fairly high evolution of high-grade dysplasia to cancer. In our series, 32 percent of the patients evolved to cancer over an 8-year period of surveillance, whereas in the Reid study, 59 percent of their patients evolved to cancer over 5 years. There may be some selection bias in this because these all tertiary referral centers likely to get the worst cases.

The Schnell study in the middle comes from the VA in Chicago, and they have the lowest incidence of cancer in the literature, but they excluded all patients who developed cancer in the first year. If you included those patients, their incidence would be fairly comparable to the rest of the series, but they wanted to look at just incident cancers so if you exclude those that develop in the first year, they had a 16 percent incidence of cancer over the following 7.3 years of follow-up.

Now, as far as the role of proton pump

inhibitors in the management of patients with Barrett's esophagus is concerned, the general consensus among physicians is primarily it's used to control reflux symptoms. There is evidence to suggest that it decreases inflammatory atypia as well, and there is experimental evidence that acid can produce epithelial proliferation in culture and even in patients. However, the effect of anti-acid therapy as a chemopreventative has not been studied in humans.

Now, the control of acid for ablative therapy has also been well known. We know we have to do something to change the constituents of the refluxate to prevent metaplasia from reoccurring. However, the degree of acid control necessary has also not been established. There have been at least two prospective, randomized trials published in the literature that have found that whether or not acid control is achieved, the degree of ablation is unchanged.

Now, these are the current management guidelines published by the American College of Gastroenterology. This is from their Practice Committee authored by Richard Sampliner.

Now, for patients without dysplasia, the group on the top line, it's recommended that a follow-up endoscopy be done in 1 year. If it is negative, then the

patients are said to follow a surveillance program of endoscopy every 3 years. Because the risk of cancer is so low, nothing is advised further than surveillance for management of these patients.

For patients with low-grade dysplasia, which would be the highest grade determined on a repeat endoscopy 1 year later, endoscopy would be advised at yearly intervals until no dysplasia is found. Once again, the incidence of cancer in these patients is thought to be fairly low and only surveillance is warranted.

Now, with high-grade dysplasia, the current guidelines recommend that that specimen be sent out for review by an expert pathologist. If confirmation is received that this is indeed high-grade dysplasia, an immediate repeat endoscopy is warranted with biopsies to rule out the presence of a concomitant malignancy.

Now, they did break this down a little bit further into categories. These were established at our institution and have really not been prospectively validated. Now, with uni-focal high-grade dysplasia, which we define as less than 5 aberrant crypts in one biopsy assessment out of an entire surveillance set, this was found to have less chance of progression to malignancy, and therefore the group felt that surveillance or possibly intervention was warranted. If you have more than this

small amount of high-grade dysplasia, it was termed multi-focal and intervention is required, either endoscopic or surgical. And finally, if there's any evidence of mucosal irregularities such as nodularity, ulcers, or strictures, then intervention with esophagectomy or endoscopic therapy was recommended.

Now, the management of high-grade dysplasia in Barrett's esophagus currently for the patient involves three choices. First, confirmation that the biopsy truly contains high-grade dysplasia. After this is established, we always tell the patient there is a chance of concomitant cancers, and it may be as high as 40 to 75 percent that we just can't find with initial endoscopy. Given this scenario, the patient can still continue to undergo surveillance --so-called active surveillance has been promoted by the group in Chicago -- endoscopic ablative therapy, which obviously we're here to talk about today, or surgical resection.

Now, for the patient, this entails several drawbacks with each of these proposed methods of treatment. With surveillance, there's a constant worry that with every follow-up endoscopy, they may be told they have cancer, not to mention the inconvenience of going in to see your local gastroenterologist every 3 months for these procedures.

With endoscopy therapies, there's a possibility

that the therapy is not complete, that the risk is not eliminated, and as you'll hear about later, there are several known complications.

And finally, with surgical therapy, this is a major operation with significant mortality and morbidity, which many patients in this age group -- and by the way, Barrett's presents itself usually in the fifth and sixth decades of life, at least Barrett's with high-grade dysplasia. So these are generally a little bit older patients. This could be quite a challenge.

The guidelines for esophagectomy. These are summarized by Tom Demeester and placed into this slide. This was an article that he wrote for one of the surgical journals. Basically he thought that the candidates that were best suited for esophagectomy were those that were less than 75 years of age, had an ejection fraction of greater than 40 percent, and an FEV pulmonary function of greater than 1.25. So basically reasonable cardiac and respiratory function and not too old of a patient. If that patient fulfilled those criteria, then they were surgical candidates and should undergo further evaluation for actually metastatic cancer. That's why EUS, endoscopic ultrasound, and CT scans of the chest and abdomen were recommended.

Now, if you don't find any evidence of

metastatic disease, then the patient could undergo esophagectomy, of which there were several techniques, transhiatal or transthoracic, and also a new one promoted by Dr. Demeester, vagal sparing.

Otherwise, the patient could be considered for endoscopic ablative therapy. Obviously, if the patient was not a good surgical candidate, endoscopic ablative therapy would play a greater role.

Now, recently there was a study published from Johns Hopkins University with their experience with prophylactic esophagectomy just for high-grade dysplasia in Barrett's esophagus. This does not include any individual cancers which a lot of the series have published. It's an experience with 60 patients. Overall, over this long period of time, almost two decades, their operative mortality rates weren't too bad. They're a little less than what's reported for esophagectomy, but still range about 2 percent and really hasn't changed much. The complication rates are about 29 percent, and these are fairly significant complications, very severe strictures, anastomotic leaks, infections, and so forth.

Interestingly enough, as I mentioned, there's this occult adenocarcinoma that we endoscopically can't detect, but it actually has been dropping at the Johns Hopkins institution from 43 percent in about the first

decade to about 16.7 percent more recently. We believe those factors have to do with protocols for standardized regimens or for biopsying Barrett's and also for improvement in the technology. We now use video endoscopes which magnify the esophagus versus the old fiber optic systems.

Most recently at our annual meeting in May of this year, a decision analysis was performed by the group at the University of North Carolina. Now, this is unpublished data. It was just presented at this meeting. But what they looked at were three different strategies for treatment of patients with high-grade dysplasia. One strategy was observation. One was ablation using photodynamic therapy and data taken from Dr. Overholt's center, and the third was surgical resection.

Overall, what they found out was that the ablation strategy was the most effective and that's illustrated in this curve here. On the y axis is actually quality adjusted life years saved. That's, I guess, a typical cost efficacy outcome. And the higher the bar, the better the result. As you can see, ablation dominates effectiveness, with observation coming in second, and actually surgical resection coming in last probably because of the drop-off in quality of life.

Now, the observation arm was actually the most

cost effective, basically that you're not doing any major intervention, and that comes out at $2,319 per quality adjusted life year. It's cheaper obviously because the endoscopic arm with ablation includes surveillance afterwards. It was not thought that these patients would go on and not ever have endoscopy.

And finally, ablation therapy, in addition to observation, added $13,226 per quality adjusted life year, which is within the realm of several prevention strategies like Pap smears and so forth. So it was thought to be a fairly cost effective approach.

At this time, I'd like to turn over the podium to Gene Overholt who was the principal investigator of this multicenter trial. Gene?

DR. OVERHOLT: Thank you, Dr. Wang. Mr. Chairman, members of the committee, and guests, I'm Bergein Overholt, Medical Director of the Laser Center of the Thompson Cancer Survival Center in Knoxville, Tennessee, and on behalf of my 27 co-investigators, it is my privilege to introduce to you the results of the study on the efficacy and safety of Photofrin PDT for the ablation of high-grade dysplasia in Barrett's esophagus.

This is the pivotal study, the phase III study. There are supportive studies, a phase I/II and the phase II, from the Thompson Center, but today we'll be discussing

our pivotal study on PHO BAR 01, the phase III clinical trial.

This was a phase III, multicenter study, blinded for efficacy; that is, the pathologists were blinded. It used a central pathology laboratory, and there were 30 participant sites primarily in North America and in Canada, and with one in France and two in the United Kingdom.

The primary objective of the study was to assess the efficacy of Photofrin PDT plus omeprazole in producing complete elimination of high-grade dysplasia in patients with Barrett's esophagus compared to omeprazole alone.

The secondary objectives were to assess the complete elimination of all Barrett's dysplasia and metaplasia and all histologic grades of dysplasia.

Secondary objectives included duration of the response, time to progression to cancer, time to treatment failure, and survival time.

The power of the study was based on the primary objective -- and that is complete elimination of high-grade dysplasia -- and the secondary objective, time to progression to cancer.

Patients with an established diagnosis of high-grade dysplasia were referred to one of the 30 sites. They

underwent informed consent and then screening endoscopy which consisted of 4-quadrant, large particle or jumbo particle biopsies every 2 centimeters over the entire length of the existing Barrett's esophagus. If the biopsies were proven in the central pathology lab to show high-grade dysplasia in Barrett's, the patients were then randomized 2 to 1 with 2 patients going to the Photofrin PDT plus omeprazole 20 milligrams b.i.d. treatment arm versus the control arm of omeprazole 20 milligrams b.i.d.

The study design for those who were treated with photodynamic therapy included the institution of omeprazole b.i.d. therapy 2 days before. On day 1, patients were administered Photofrin intravenously at 2 milligrams per kilogram, and on day 3 they underwent light exposure using the lasers that were shown to you earlier. On day 5, they were reexamined and any skip area in the field of treatment could be retreated at that particular time. Patients could undergo a maximum of three courses of therapy at 3-month intervals between the original treatment.

After randomization and treatment, patients underwent continuous endoscopic surveillance every 3 months. However, if there were four consecutive quarterly endoscopic biopsy exams that were negative for high-grade dysplasia, they could then be followed at 6-month

intervals, with again the primary endpoint of evaluation and power being the elimination of high-grade dysplasia.

Now, there were three response levels. The first was CR3 or better, which was the primary endpoint of complete elimination of high-grade dysplasia. CR2 or better included elimination of all histologic grades of dysplasia, and CR1, the superior and the best response, was complete replacement of all Barrett's dysplasia and with complete replacement of all Barrett's by normal squamous epithelium.

The primary endpoint again was the proportion of patients who achieved complete elimination of high-grade dysplasia determined by histopathology after a minimum of 2-year follow-up, subjected to the Fisher's exact test statistically.

The secondary endpoints included the proportion of patients who achieved complete replacement of all Barrett's dysplasia and metaplasia with normal squamous epithelium and the elimination of all histologic grades of dysplasia, both subjected to the Fisher's exact test. Secondary endpoints included duration of complete response, time to progression to cancer, time to treatment failure, and survival time as determined by the Kaplan-Meier method.

485 patients were referred for screening. Of those that were eligible for randomization, the 208

patients, 138 were randomized to the Photofrin PDT/omeprazole treatment arm and 70 to the control omeprazole only arm.

The groups, in terms of demographics, were very comparable with a mean age of 66, predominantly males, predominantly caucasian, and the smoking history in both groups was comparable at 64 percent. This really is representative of the disease population that we see in practice.

Now, the extent of high-grade dysplasia in Barrett's at the baseline was comparable in both groups. In the PDT group, there were 36 percent of patients who had high-grade dysplasia at a single focus and 39 percent in the omeprazole only group, whereas there were 63 percent of the PDT/omeprazole group that had multi-focal high-grade dysplasia and 61 percent in the omeprazole only. So the groups were comparable, but this is significant disease.

The endoscopic findings at baseline exam were also of interest. Hiatal hernia is prevalent in both groups. One-third of patients, 33 percent, in the treatment arm and 27 percent in the control arm had nodules at the time of the baseline endoscopy, and there was a small percent with ulcers and esophageal strictures.

In terms of the patient disposition, 485 screened, 208 randomized, 138 for the ITT in the treatment

arm, PDT plus omeprazole. The safety population, there were 133 that were evaluated for safety, and 130 patients were evaluable for the study. In the omeprazole control arm, 70 for the ITT, 69 for the safety population, and 69 for the evaluable population.

In terms of the screening, there were 277 failures, and Dr. Bronner will discuss this further, but no high-grade dysplasia was found in 237 of these patients, a rather remarkable finding. A small number, 13, failed screening inclusion and exclusion criteria, and 25 declined participation.

Again, the primary endpoint was CR3 or better, that is, absence or elimination of high-grade dysplasia.

The ITT population at the end of the 2-year minimum follow-up shows highly statistically significant favor toward the Photofrin PDT group, with 77 percent being clear of high-grade dysplasia compared to the control group of 39 percent. But it's also important to notice on this slide the difference at all points, 6 months, 12, 18. There is a wide variation between the response in all groups. This is a highly significant finding.

Secondary endpoints. Let's look at these. The quality of complete response. For the CR2 or better and the CR1 or better, likewise highly statistically significant improvement in favor of Photofrin PDT with no

dysplasia in 59 percent of patients versus 14 percent in the control. In fact, there was elimination of dysplasia and replacement by a squamous epithelium in 52 percent of the treatment arm versus 7 percent of the control, statistically significant at less than .0001.

Duration of complete response, defined as the period in days from the day of the first documentation of a response until the day of the first documentation of the loss of the response.

The Kaplan-Meier curve for the CR1 response censored shows the curves with a median time for the treatment group of 316 days and the control group of 84 days, a wide discrepancy here.

For the CR2 group, the median time was 478 days, and for the control group it was 184 days.

For the CR3, which was the primary endpoint, there is wide discrepancy. This is the treatment arm and the control arm, with a median time of 987 days for the treatment and 98 days for the control, one-tenth of the time.

In terms of that being summarized on table form, the CR3 or better responders, 77 percent in the treatment arm versus 39 percent in the control arm. But again, a median CR3 or better response in terms of duration was 987 days for the treatment arm compared to 98 days for

the control arm. This is one-tenth or 10 times the difference in this.

Progression to cancer. This is an important one. The proportion of patients progressing to cancer, again statistically significant in favor of the Photofrin PDT group. 28 percent of controls progressed to cancer over the follow-up of the 24-month follow-up versus 13 percent in the treatment arm, statistically significant at .006.

The time to progression to cancer also is statistically significant in favor of the PDT group, as you can see, at a p level of .0014.

Time to treatment failure, defined as the progression of high-grade dysplasia to cancer or the start of any intervening therapy for high-grade dysplasia other than the randomized study treatment, and this data was censored at their last efficacy assessment. Again, statistically highly significant in favor of Photofrin PDT. This is the K-M curve for the treatment group and the control group, significant at a level of less than .0001.

Survival time was essentially equal for both groups, as there were very few deaths.

Now, let's move on to safety, and you're all interested in this, of course, because this is where patients are treated. In terms of the first group here,

those that were evaluated for safety, 133 in the treatment arm and 69 in the control arm. Adverse events were common in both groups. Associated adverse events were, of course, more common in the PDT treatment group. The serious associated adverse events, 12 percent in the treatment arm versus 1 percent in the control arm.

Now, there were 3 deaths that were recorded. None of these were disease-related. None of these were treatment-related. There was 1 PDT patient who expired with breast cancer, 1 who expired after CABG surgery, and there was 1 in the control group that suffered a stroke and expired from that.

The common adverse events: photosensitivity in 68 percent, vomiting in 38 percent, strictures in 36, constipation, noncardiac chest pain, and fever. Whereas in the control group, 12 percent with noncardiac chest pain and 10 percent with diarrhea.

In terms of photosensitivity reactions, as judged and assessed by the treating physician, 69 percent were mild. Now, there were a total of 223 events, so that a number of patients had more than one event. 69 percent mild, and we would define this as redness of the skin, a mild sunburn. And 24 percent were moderate, that is, a sunburn with some edema; and 7 percent as severe, sunburn, marked edema, even progressing to the point of blistering.

A few of these patients healed with some scarring of the skin tissue. This is something that we now put a great deal of emphasis on in terms of education of patients to avoid photosensitivity. It's an inconvenience for the patients, but considering the alternative therapy, that is, esophagectomy, this is a minor inconvenience for these patients in our experience. These all healed. None required hospitalization, and the patients are doing well.

Esophageal strictures. 36 percent of patients in the treatment arm had esophageal strictures or developed those versus 0 percent in the control arm. 8 of this group developed them with one course of therapy, an additional 22 percent if there were two courses of therapy, and 5 percent more if there were three courses of therapy. Multiple courses are associated with treatment field overlap, and when you treat one field and treat the next field, you get an overlap, so you ultimately got a double dose on that treatment field, making it more prone to develop an esophageal stricture.

The intensity of these strictures, again as assessed by the treating physician, mild in 29 percent, moderate in 51 percent, and severe in 16 percent of the patients. Those patients required dilation for relief. 12 required one or two dilations. 8 required 3 to 5. 14 required 6 to 10, and 15 required more than 10, but all

patients are swallowing solid food and eating well and doing essentially quite well in terms of their swallowing.

So let me conclude. Photofrin PDT is significantly more effective than omeprazole only in the elimination of high-grade dysplasia in patients with Barrett's esophagus after a 2-year follow-up at a p level of less than .0001.

Second, the proportion of patients progressing to cancer in the Photofrin PDT/omeprazole group is significantly lower than those in the omeprazole group after the 2-year follow-up, again at a p level of .006.

Third, patients in the Photofrin PDT and omeprazole treatment group experienced a significant delay in the progression to cancer, a p level of .0014.

Fourth, there was no treatment-related death reported.

Fifth, the most frequently reported adverse event occurred in 68 percent of patients in the treatment group and that was photosensitivity. 93 percent of those were mild to moderate and all patients have healed satisfactorily.

Sixth, 36 percent of patients in the treatment Photofrin PDT plus omeprazole group developed esophageal strictures. All were manageable through dilations.

Thank you. And now it's my opportunity to

introduce to you Mary Bronner, Director of the GI and Hepatic Pathology Department and Professor at the Cleveland Clinic in Cleveland.

DR. BRONNER: Thank you, Dr. Overholt.

Ladies and gentlemen, thank you for your attention to the pathology issues in this trial of photodynamic therapy in Barrett's esophagus.

Now, why is pathology important? The main concern is that pathology is required for the definition of Barrett's esophagus and absolutely required for the identification of precancerous change. We term the precancerous change dysplasia and we grade it. That's the primary role of the pathologist at the microscope looking at biopsy material.

So the definition requires two components, as Dr. Wang has already pointed out. Not only do you need an endoscopic abnormality of columnar mucosa in the esophagus, but you also have to have biopsy documentation that it is a particular type of epithelium. We term it metaplastic columnar epithelium with goblet cells, or intestinal metaplasia.

This slide shows you an example of Barrett's metaplasia and at the very beginning phase of neoplastic progression within Barrett's as it proceeds towards cancer or low-grade dysplasia. So this half of the slide

demonstrates Barrett's esophagus but negative for dysplasia. It has no precancerous changes, and this half of the slide shows the early stages of precancerous dysplasia.

Notice the great variation in the nuclei. The nuclei are these dark blue/purple structures. They are the sites of the DNA within the cell, the sites of the chromosomes and the genetic material. And they become abnormal as cells proceed towards cancer. The nuclei become abnormal. So you can see that the nuclei over on this half are quite small. They're all single and basally oriented within this epithelium. Down towards the base of the epithelium is where the nuclei normally reside. Whereas, on this side we see the nuclei beginning to enlarge, to stratify or stack up on top of each other. But note that these nuclei are still quite orderly. The long axis of the nuclei remains perpendicular to the basement membrane which defines where the epithelium ends and the sub-epithelial tissue or lamina propria begins.

So this is maintenance of nuclear polarity. This is negative. This is low-grade dysplasia.

High-grade dysplasia, on the other hand, shows a progression of these nuclear abnormalities. The nuclei are more disordered than in that case of low-grade dysplasia you've just seen. They develop more nuclear

enlargements, more nuclear chromasia, hyperchromasia, which is how darkly they stain on this particular hematoxylin and eosin stain. And they're quite disordered relative to the basement membrane, as I pointed out before. These nuclei no longer are perpendicular. They're much more jumbled and disorderly, and in addition to the cytologic changes relative to the nuclei, the architecture is much more disordered in high-grade dysplasia as well. So this combination of features allows pathologists to categorize the varying phases of dysplasia.

The next slide illustrates the final step in neoplastic progression, and that is actual invasion or development of adenocarcinoma, cancer. So these cells here, which are highlighted by these black arrowheads, are all individual cancer cells that have escaped from the epithelial confines. They've invaded beyond that basement membrane that delimits the epithelium from the stroma, and they are now infiltrating within the stroma. This is the very earliest phase of carcinoma where it's in the mucosa, and it will then proceed to invade more deeply and to metastasize. But once the cells escape into the stroma here, they are malignant and they have the competence. They developed a capacity to metastasize.

So that's the job of the GI pathologist in the diagnosis of Barrett's esophagus and neoplastic progression

within the esophagus.

Now, the three photomicrographs I've shown you as examples are classic examples. They're very straightforward. They're at the end of the bell curve for each one of their categories. It's not always so straightforward. As in many things in life, it's much more complex and certainly that's the case in the grading of dysplasia in Barrett's esophagus. The reason is complex, and I'd like to take you through some of the difficulties that we face.

However, I'd like to point out at the outset that expert GI pathologists are well aware of these problems and are able to deal with them and achieve excellent diagnostic uniformity at the high end of the neoplastic spectrum or high-grade dysplasia and cancer, which is the important end where these severe therapeutic interventions become an issue. So GI pathologists do very well at the high end of this spectrum. And let me show you some of the problems.

First of all, Barrett's epithelium within a Barrett's segment inside of a patient's esophagus is not always intestinal metaplasia with goblet cells. It's an admixture of cell types, not only goblet cells but also gastric type epithelium. And gastric type epithelium or gastric cardiac epithelium can take on a very atypical

appearance when it becomes irritated by reflux disease. The inflammation and the toxic components in the refluxate that enter from the stomach into the esophagus, composed of bile and acid and pancreatic juice, are quite irritating especially to gastric type mucosa. The intestinal type mucosa of Barrett's tends to be more resistant, but the gastric type mucosa may become quite atypical and simulate all the features of dysplasia. So the GI pathologists know how to recognize the gastric mucosa -- there's a number of very specific differences -- and can avoid that trap.

The next trap is the atypia of metaplastic epithelium that's limited to the basal glands. Now, the basal glands of any intestinal mucosa that are deeper into the bowel wall as opposed to the very surface epithelium -- that's what I'm talking about is basal. Those basal glands of any intestinal epithelium are where the progenitor cells are, the dividing cells, the proliferative zone of that epithelium. It turns over every 2 to 3 days. So it's a highly replicative and proliferative epithelium. So that basal zone is always activated and it's characteristically cytologically atypical. The GI pathologist knows that -- that's just normal histology in intestinal epithelium -- and knows not to over-interpret that basal zone as dysplasia. So that's another pitfall to be avoided.

Another pitfall is inflammatory atypia.

Inflammatory atypia is the bane of surgical pathologists, not just in the esophagus but everywhere in the body. It's something that needs to be factored into the assessment of neoplastic change. Certainly Barrett's is a prime concern because it's principally an inflammatory disease caused by gastroesophageal reflux. So that's a big problem that can be avoided with recognition.

Sampling error is a serious issue with any neoplastic surveillance program. The problem is that we're only sampling a small minority of the epithelium when we take biopsies. So even though we're taking 4-quadrant biopsies intensively at every 2 centimeters throughout the Barrett's segment, we're only sampling less than 5 percent of the entire surface area. You combine that less than 5 percent sampling with the fact that dysplasia is often very focal within the entire field of Barrett's epithelium. So you combine those two factors and obviously you're going to have difficulty detecting these lesions from sampling error. So that's another problem.

Nuclear polarity, as I've tried to illustrate to you on those two photomicrographs of low and high-grade dysplasia, is our most objective criterion to separate low- and high-grade dysplasia. It's under-utilized by many pathologists as a criterion.

Morphologic spectrum. As I've already

mentioned to you, in any biological system and particularly as cells proceed toward cancer, there's a morphologic spectrum of change. One cannot precisely define the boundaries. It's a combination of thousands of different features that are being collated by the pathologist's mind. Is this severe enough alteration to separate low- and high-grade dysplasia? Is this negative for dysplasia or is this atypia enough to make it low-grade dysplasia? Are these cells really invading the lamina propria or is this inflammatory destruction? So the boundaries are blurred and that makes it a difficult issue as well.

But with experience and a continual high volume exposure to this material, this type of histologic material, GI pathologists are actually excellent at separating these changes, especially at the high end of the spectrum, as I'll show you in a moment. So experience and volume are the key elements.

The FDA recognized that this was a problem, pathologic agreement on diagnoses. Early on, they mandated a rater study to assess whether the three pathologists who were reviewing all the material for this PDT trial could agree with each other on the diagnostic assessments. Three pathologists were necessary for this trial just because of its scope. To date the three pathologists, who include myself, the late Dr. Rodger Haggitt, and Dr. Shari Taylor,

have reviewed over 30,000 glass slides thus far in this trial. So one person couldn't do it by themselves. We needed at least three observers.

But the FDA wanted to know are these three people equivalent and can they accurately assess these diagnoses. So the rater study undertook assessment of this and you can assess agreement statistically looking at percent agreement or kappa statistics, which are both analyzed here, and let me explain them to you.

You have to look at the slides twice, so round 1 and round 2, in order to assess whether an observer agrees with himself, so intra-observer variability. So we not only had to look at these slides originally, we had to look at them again. The agreement is excellent to outstanding actually. There are no medical assessments in the literature, be they radiologic or clinical or pathologic, that have percent agreements that are really quite this high. These were outstanding results I'm happy to report. It was a nerve-racking situation until we got the data back. We were very happy to know that we performed well.

And the kappa statistics are a different biostatistical measure. A statistic of more than .8 is near perfect agreement so that the inter-observer variability between the three pathologists was near perfect

and the pathologists amongst themselves, how well they agreed with themselves, ranged from near perfect to excellent, but this difference was not statistically significant. So the pathologists did quite well in the confines of this particular study. Now, these three pathologists all worked together for many years, so it's no surprise that they shared diagnostic opinions.

The next slide illustrates a recommendation by the American College of Gastroenterology which Dr. Wang has already pointed out that deals with the fact that although three GI pathologists at one institution may agree with each other extremely well, that may not be generalizable to the entire group of anatomic pathologists making these diagnoses across the country. So all of those difficulties that I've pointed out, taking all of that into account, a very wise recommendation by the ACG was that a diagnosis of high-grade dysplasia, given its serious clinical consequences, should be confirmed by an expert GI pathologist. So it has serious consequences and it's a difficult diagnosis. So it makes sense that it should be confirmed by somebody who has a high volume experience.

The next slide illustrates how that recommendation applies to this particular study of photodynamic therapy. Specifically in the screening phase when we were trying to identify 208 patients who entered

into the trial, we had to screen a total of 485 patients to find the 208 that actually fulfilled the protocol requirements.

So what happened to the rest? 237 did not meet the protocol requirements and these are the varying diagnoses other than high-grade dysplasia in Barrett's that the study pathologists derived after an additional endoscopy was performed under protocol conditions with the appropriate sampling degree and by one of the study investigators. So these are the diagnoses based on the protocol baseline endoscopy. We did not go back and review the original pathology from the variety of outside hospitals, varieties of histologic preparations in laboratories. We did not go back and review that.

So what that means is that this number somewhat overestimates the true difference in diagnosis. Some of it is from sampling error. We didn't review these original 237 biopsy sets, and some of them would have picked up focal dysplasia that was in fact present that wasn't picked up on the follow-up endoscopy because of the sampling error problem. So it is somewhat of an overestimation of the diagnostic discrepancy. There is sampling error at play here. We know that from the biology of Barrett's esophagus.

How much? I can't say because we didn't

undertake a review. We wanted to get as pure a population of patients with Barrett's and high-grade dysplasia all studied with a similar protocol endoscopy and similar histology laboratory preparation and similar histopathologists. So to generate that pure population for scientific validity, that's what the protocol requirement was.

But it does point out that there is a potential for serious diagnostic error on the part of pathologists in terms of how these patients get classified, and that's why the ACG guideline is so important that these diagnoses be reviewed by an experienced GI pathologist.

The next slide shows that there's hope. As I said, pathologists actually can show a great deal of skill and agreement at the upper end of the dysplasia categorization so that in this study of 12 expert GI pathologists from academic centers all across the country -- these people did not all work together at the same institution. They're all from different institutions. When we look at the diagnostic groups of anything less than high-grade dysplasia, Barrett's, indefinite low-grade, compared to anything, including high-grade dysplasia and above, carcinoma, that's the important clinical dividing line in terms of management decisions.

The kappa statistics for inter-observer

variability were excellent at .7, and for intra-observer variability, how well the pathologists agree with themselves, it was near perfect. So expert GI pathologists who do see a high volume of this material on a continual basis are qualified to make these diagnoses and can do it quite accurately.

And with that, I will end the pathology discussion and turn it back over to my colleague, Dr. Martin.

DR. MARTIN: Thank you, Dr. Bronner.

Before formally concluding this presentation from our group here, allow me please to just summarize briefly the supportive studies that are also present in our submission, and my intention is to present the integrated summary for efficacy and safety in this disease indication, high-grade dysplasia.

This was the clinical development program that we had, and three clinical trials composed our submission: a pivotal trial, which was presented by Dr. Overholt, and the two supportive studies that were investigator-sponsored trials originating from the Thompson Cancer Survival Center in Knoxville and conducted by Dr. Overholt.

The first study, which was accomplished as of 1993 up to 1998, had the objective to evaluate the safety and efficacy of PDT in Barrett's esophagus patients with

dysplasia or early adenocarcinoma to determine light dose. So it was a dose-ranging study. All patients received PDT plus omeprazole but different light dosing ranging from 250 to 300 joules per centimeter. So the design was an investigator-initiated, partially blinded, uncontrolled. The enrollment for this study was 99 patients.

The second study was to evaluate the incidence and severity of stricture between PDT in patients receiving steroids versus PDT alone in dysplasia and adenocarcinoma in Barrett's esophagus, and this study design was to demonstrate a potential or look for a potential effect of steroids in diminishing or reducing the incidence or severity of stenosis. Patients received either PDT plus OM with or without steroid. Again, it was an investigator-initiated, partially blinded, randomized, controlled study, and the enrollment for this study was 87 patients.

So if we integrate and cumulate all patients having received PDT therapy, either for HGD or for other conditions, including other extensions of dysplasia or early carcinoma, we see that we have a cumulative number of 224 patients who received PDT plus omeprazole with the HGD condition and we have 100 patients having received PDT here for other conditions. This is the control group of our pivotal study.

The overall clinical response when cumulated

and specifically looking at the CR3, or the complete ablation of HGD or better, response from our pivotal trial, you still see the figures, 77 percent positive response versus 39 percent positive response for the omeprazole group. And in the two other studies, each one had a very high efficacy in ablating HGD up to 93 percent or 95 percent, and if we integrate all those data, PDT for the ablation of high-grade dysplasia gives a very high positive response of 83 percent.

What is more important perhaps or at least very confirmative of the efficacy of this treatment modality is the duration of response in number of days as depicted in our pivotal trial that is high, up to 987 days. So you understand then that we have patients that have been in the trial for a minimum or median number of years, 3.5 years.

The omeprazole response is also present. There is some regression of high-grade dysplasia, but the duration of this response does not exceed 3 months. We could not find this duration of response in this study, but in this supportive study, 390 days was also a long-term duration of response.

Again, if we integrate those data, the duration of response for the PDT treatment is 672 days which is very significant as an outcome for this therapy.

The safety profile. Again, if we cumulate all

patients who received PDT for the high-grade dysplasia indication, we can cumulate 219 patients in the HGD plus the omeprazole group coming from our pivotal study, and you see that the adverse events, when cumulated, are present in 99 percent of patients having received PDT, the associated adverse events are also very high, and you will understand that photosensitivity and strictures do account for the high associated adverse events. They are much less, of course, in the OM group.

Serious adverse events are present to 29 percent, and you've heard the clarification on severity of either stenosis, strictures, or photosensitivity, and this accounts for that number. But you also see some serious adverse events depicted in the OM group alone.

Serious associated adverse events account for 11 percent, and again this comes from the severity that was described earlier for some patients with severe photosensitivity and the severe stenosis, all conditions manageable, not leading to permanent conditions.

There were 4 deaths in the HGD-PDT group. There were 2 in our pivotal study; 2 come from the supportive studies. None are disease-related or therapy-related, more specifically of PDT therapy.

The common adverse events are regrouped by system. A lot of them more so into the HGD-PDT group are

in the GI system. You can expect that with the strictures, and also common symptoms encountered in most studies, diarrhea, nausea, et cetera are different in the OM group on account of the intervention imposed on patients receiving PDT. Skin, of course, is a system that is touched by this PDT therapy, namely photosensitivity. And the rest are not necessarily enlightening onto the absence of safety of this therapy.

In conclusion, Mr. Chairman and committee members, I think we have demonstrated the effectiveness of PDT Photofrin in ablation of HGD in Barrett's esophagus. The absolute risk reduction in progression to cancer after 2-year follow-up is 15 percent. That is the difference of incidence of progression to cancer in both groups in favor of the PDT group. The patients we heard can be adequately identified through labeling based on current diagnostic guidelines. Adverse events, including strictures, are manageable. And this novel treatment modality represents to our sense an acceptable alternative to current therapeutic options for the treatment of this premalignant condition, high-grade dysplasia in Barrett's esophagus.

I thank the committee for their attention and interest in our presentation. Thank you.

DR. WOLFE: Thank you, Dr. Martin. I'd also like to thank Dr. Wang, Dr. Overholt, and Dr. Bronner for

their excellent presentations.

We're doing very nicely and I want to continue on. I want to make a couple of comments first before we open up the questions for the panel to ask the sponsor. The comments are the following.

First of all, this is very nicely done scientifically as a study. But I want to stress a couple of points.

Dr. Bronner very carefully pointed out how difficult it is for the pathologist. I don't want to minimize the difficulty for the average gastroenterologist. The toughest place by far for a gastroenterologist to biopsy within the GI tract is the lower esophagus. Let me explain why.

You're down at the bottom of the esophagus where the diaphragm is. The person is breathing hopefully.

(Laughter.)

DR. WOLFE: As a result, the esophagus is moving up and down. We're coming in through a scope, look tangentially, trying to hit a target. Once you hit a target of biopsy, there's blood everywhere, and it's very difficult to see. So this is not an easy procedure. For me it's sometimes the most frustrating part. Even though it's relatively easy to get down there and do, it's just very hard to biopsy accurately. And sampling error is not

trivial at all. We're doing a 7 millimeter biopsy of an area which is much, much larger.

That's maybe one of the reasons you see some of the differences later on because this is the largest number of patients on medical therapy only I've ever seen who regressed, and I really question that. I think sampling error really has to be brought in as a possibility.

I'm getting old so I like to make all these general comments and philosophical comments. Someone asked me a long time ago, what makes a good physician? And a good physician is someone who knows his or her own limitations and is not afraid to seek consultation with either colleagues or others.

Just as GI pathology is a specialized area, so is gastroenterology. In the case of GI pathology, it is very, very specific. I don't think any person here would go to, for a clinical problem, say, a serious problem with reflux disease or diarrheal illness, to a generalist. You'd go to a gastroenterologist. The same thing here. With a diagnosis so difficult to make, which requires real accuracy and expertise and a lot of experience, this is something in the purview of a gastrointestinal pathologist. I gained a lot of respect for this when I was at Brigham and Women's Hospital when Jim Madara and others were there. It was an excellent GI pathology group.

Now, I'm going to start along those lines. I'm going to ask a question because one of the problems is that people don't realize their limitations and they may think I can diagnose this. I don't need a GI pathologist. Do you have any other evidence? Was any study done just taking some general pathologists to do the same study you did to show that they did not have that degree of inter- or intra-observer agreement?

DR. MARTIN: Dr. Bronner?

DR. BRONNER: Thank you for that question. I would point to actually the results of the screening phase as the best available data that I know of in the literature, looking at the ability of general pathologists from the community to make the diagnosis of high-grade dysplasia in Barrett's esophagus.

DR. WOLFE: That's not exactly the same, though. That's where you disagree and you had the expertise. But I think it would be very valuable just to show the general pathologists that they don't have the means, the tools, the proper experience that you do, that they cannot really agree with each other and they don't agree with themselves either, if you look at the intra-observer variation.

DR. BRONNER: Exactly. I think that would be an important study to conduct.

The other piece of evidence that I would point to is that general pathologists I believe do recognize that this is a difficult area and that it's fraught with diagnostic issues. The reason why I say that -- not all, of course. But I think the community is improving in general and that consultation is sought. Pathologists hate to make the diagnosis of high-grade dysplasia in Barrett's because they know the serious consequences. That's pulling a trigger that they don't want to pull unless they're 100 percent sure. So many people seek consultation at the level of high-grade dysplasia. My own personal consultation practice last year received over 1,000 requests for review of a diagnosis of high-grade dysplasia. So that's another piece of evidence.

But I do think pathologists need to be studied for intra- and inter-observer in the community.

DR. WOLFE: Dr. Wang, actually before you answer, I want you to consider this. Of the gastroenterologists here, how many of us get patients referred to us with definitely they have dysplasia, high-grade, low-grade, without question, and then we give it to our pathologists and they don't have it? And they've been seen by another gastroenterologist several times. We all see this. So it may be improving but it's not there yet.

DR. BRONNER: I agree. I completely agree.

DR. WANG: Yes. I just wanted to point out there was a study by Doug Rex where they took an indexed set of five slides and sent them to the community pathologists in the Indiana area and got their interpretations, something like 12 or 13 local, not GI pathologists, general pathologists, and their interpretation rates were very poor, on the average of about 30 percent agreement with the indexed biopsies.

DR. WOLFE: The advantage you have here -- you had the slides already prepared and you had the agreement in the slide preparations within your group. You can do a direct comparison.

DR. BRONNER: You're right. We should do that. We will do that.

DR. WOLFE: Dr. Levine.

DR. LEVINE: Well, Mike, I have a few more years on you, so I'm going to go back, having done Yag laser, Nd:Yag laser, having done lots of dilatations, and continue to do so.

I think you hit upon two big points here. One is we've just discussed the GI pathologist. As a matter of fact, Dr. Wang, we have a GI pathologist taking a second year at the Mayo Clinic. We have a GI resident finishing up going to the Mayo for another year in GI pathology. And there is a national shortage in GI and hepatic pathologists

to an extreme degree where at my medical center, which is an academic medical center, where we sit around at weekly conferences and debate whether there's high-grade dysplasia, low-grade dysplasia with the GI pathologist, and a cycle of about every five or six years, we lose our GI pathologist and we're without a GI pathologist. So we're the experts. And this goes on for many, many years. And even though there's a major shortage in gastroenterologists today and you can go anywhere in the country and put up your M.D. and you're busy, there's a bigger one in GI pathology. So there is a real problem.

I would complement this study in many ways. It's well organized. It's well designed. I think as Dr. Overholt alluded to, the screening group is so large and there being such a large failure rate just emphasizes the point that we really have out there in my community and your community pathologists who don't know how to read this. We have gastroenterologists who don't know how to biopsy, and in the community where more is done than in the academic medical centers, there's a potential big problem not for only the cowboys who like to do endoscopy and like to have toys to play with -- and we have that in our specialty -- but also due to the fact that this is an ever-increasing problem and we don't know how to deal with it.

I think the ACG addressed this very well, as

you alluded to in your presentation, and that is restrictions. A restriction should be followed, as well as education among our own people, in GI pathology and in gastroenterology, that this must be looked at, these slides, by a well-qualified -- i.e., GI -- pathologist.

So with that point, I think we can continue and then ask a few more questions, if I could, reemphasizing this point. I think it's a problem.

My first question is you had 133 patients in slide number 84 and yet when you add up all the number of dilatations -- you mentioned some were mild. There were 16 percent severe. If you add up the number of dilatations, there were 104 dilatations. 104 dilatations is a lot of dilatations. If you have a patient who may have had 10, as you pointed out, 6, 8, 10, that's misery. I mean, even if you're a good endoscopist, it's not a pleasant thing.

I'd like to know of the 16 percent with severe, were the 104 dilatations done only in the severe group or in the moderate group? Could you explain that a little bit further? There are two slides, 84 and I guess it must be 85.

DR. MARTIN: While the slides are being prompted on the screen, may I ask Dr. Overholt to come and comment on that and expand on his original presentation for Dr. Levine.

DR. OVERHOLT: You see the 16 percent of the strictures were severe. Can we see the slide that shows the numbers of dilations? There were 15 patients who had more than 10 dilations.

DR. LEVINE: It was number 84.

DR. OVERHOLT: Well, there were 15 patients who had more than 10 dilations, and that is the more severe group.

DR. LEVINE: There are 101 dilatations. I wondered why 101 dilatations were done.

DR. OVERHOLT: Is the slide you're referring to?

DR. LEVINE: Yes. If you add up the numbers on the prior slide.

DR. OVERHOLT: Some of these patients require --

DR. LEVINE: 104 dilatations.

DR. OVERHOLT: Some of these patients require multiple dilations, and that is an inconvenience for the patient. There's no question about it. They have to come in. They have to undergo sedation. They have to have a dilator passed. They have to come back and have repeated dilations.

But the patients are all swallowing well. They all are eating solid food, and considering the alternative

of the esophagectomy, they are all satisfied with the treatment that they've had. It's a significant improvement in that they have been able to avoid the esophagectomy and have elimination of their high-grade dysplasia.

DR. LEVINE: While you're up there, could you just answer? You alluded in the literature that in surgery, approximately 29 percent of people end up with strictures. I don't know the surgical literature very well. Are these strictures comparable if I was to advise someone to have ablation therapy or surgery? Strictures are a major, major problem. It's the worst thing we can have for chronicity. Perhaps they're transient in this case here. I don't know if you've had a long enough follow-up to say if they're truly transient or chronic. And I'd like you to answer that.

And can you tell me with the 29 percent in surgery that have strictures, what kind of chronicity is there and what is the nature of those strictures?

DR. OVERHOLT: Actually if you review the surgical literature, the 29 percent incidence was, I think, in the Hopkins group. But if you review it, it's up to two-thirds of patients who have esophagectomy have significant esophageal strictures.

My experience with the post-operative esophageal stricture is that most can be dilated relatively

easily. Occasionally, though, you get one with either staples or sutures that are in the actual anastomosis. They create an extremely difficult stricture requiring -- we've got a technique that we actually cut the stricture now, a strictureotomy, requiring extensive technical treatment and repeated dilations.

In terms of the chronicity in our study, of those patients that require more than 10 dilations, some of those -- if I could have that slide on the duration. As you can see, on the duration of the esophageal stricture symptomatology -- I'm sorry if you can't see that -- the great majority of patients are cleared within less than 6 months. There are a few that extend out here, and they will require intermittent dilations, if required. Most of these are infrequent now. They may be once every 6 months.

We have not had anybody, to my knowledge, have self-dilation in this study, but I have used that technique in my own practice. I think Dr. Wang does also. When they get out here in this group, if they require frequent weekly or every other weekly dilations, we teach them how to self-dilate, and they do extremely well with that. Considering the fact that they still have their esophagus, they're glad they can do it.

DR. WOLFE: Actually, before Dr. Camilleri, I have one related to this question. Do you have any QOL

data on that, any quality of life compared to other modalities?

DR. MARTIN: Quality of life evaluation was not part of the study design, as you may have noticed. That originated in 1997. It was less in fashion to do quality of life assessment. It's unfortunate. We would have liked very much to have those data. Although the comparator was surveillance therapy, it was less applicable to perhaps the real question you're asking, what about a different ablative therapy or even esophagectomy. So we don't have those data you understand.

DR. WOLFE: Dr. Camilleri?

DR. CAMILLERI: Thank you.

Dr. Martin, just to come back to one of your concluding statements and to, if I may, put it in perspective. The 15 percent risk reduction relative to omeprazole is, with all due respect, irrelevant because in clinical practice, the comparator in these patients would really be surgery, and I think we have to keep that in perspective.

I want to ask Dr. Wang, as well, because he's my good friend and colleague, whether he thinks that a difference in quality adjusted life years between observation and ablation and resection of .5 years makes any difference. Slide 36. I wonder whether you could

point it out to us. Slide 36 has been plotted with a number other than 0 on the y axis, so it maximizes the difference.

DR. WANG: Yes, Michael. That actually is, according to the outcomes people, fairly significant. I don't want to call this into question because it's our bread and butter and mainly everything I do in the Barrett's unit. But if you look at surveillance and what that does in terms of adding quality adjusted life years, it's down in the .05 range. So you're talking months.

DR. CAMILLERI: Thank you, Dr. Wang.

Now my serious question.

(Laughter.)

DR. MARTIN: To whom?

DR. CAMILLERI: Well, maybe Dr. Overholt. I would like you, if you wouldn't mind, to look at slide 67, 68, 69 because I think there's an important information here. If you look at the Kaplan-Meier curves, there's about 30 to 50 percent of patients who effectively don't have a very good response that's significantly different than the control arm, and because this is such a wonderful large study, so well-controlled, expert centers, I'm wondering whether you have done any further analysis to help us understand who would be a poor candidate for this therapy. I think that you are in a unique position to be

able to advise us as clinicians as to what would be the covariates or the factors that determine that sharp and steep curve in the first 100 days.

You do, of course, show us the median time, and in all honesty, you correctly state the median times because you calculated that from the time of 50 percent. But very often the 53 percent point there, for instance, would only be 160 days.

So I don't want to belabor the latter point. I think the more important point is what have we learnt from those people who appear not to be good candidates for this therapy? Because that's what's really important for clinicians who take this on. Thank you.

DR. MARTIN: Thank you for this tough question, as you announced it. Who would like to take that? Perhaps Dr. Donner, biostatistician, will give us his views on numbers and the they were analyzed.

DR. DONNER: No. The duration of the response, of course, was a secondary endpoint in the trial and it's not a comparison that is protected by randomization because we're comparing responders. But I agree that this would be a very important analysis to do in order to identify those patient characteristics that, in fact, do lead to a longer response. Thank you.

DR. CAMILLERI: Or just to flip it around, a

shorter response, which would then tell us not to treat those patients. Is that fair, sir?

DR. DONNER: Yes, it is.

DR. CAMILLERI: Thank you.

DR. WOLFE: Any more questions?

DR. KELSEN: Sort of looking at the other side of that Kaplan-Meier curve, because I was interested in the durability of the control, because as I look at the demographics, although the median age was 65 -- and even those patients have a fairly long life expectancy -- a number of patients are in their 30s and 40s. How durable is complete control of Barrett's? Do you have any more follow-up as you look at the slides? Because as I look at the Kaplan-Meier curves, they're flat, and what it sort of suggests is if you achieve complete control, you have a tail on the curve that doesn't relapse. Are you surveilling them continually now? Is this being maintained?

DR. MARTIN: For several patients, they are still followed up and maintained in therapy, and they are followed up for longer periods. The median is 3.5 years and we have submitted those patients into a prolonged study. The same study population is being evaluated for a period of 5 years. This is the PHO BAR 02 study.

I will ask Dr. Donner to come and comment on

the Kaplan-Meiers and the probability of maintaining such a remission. That explains in part the maintenance or the flat curve at that moment. Could you please comment on that, Dr. Donner?

DR. DONNER: Could you repeat the question?

DR. KELSEN: I think the essence of my question is, does this therapy permanently and completely remove the risk of the development of high-grade dysplasia? The presumption would be that a patient undergoing esophagectomy -- I'm not sure we even know this, but it's assumed that a patient undergoing esophagectomy has had a definitive curative procedure, will not develop high-grade dysplasia, and will not develop carcinoma. So if we assume that -- we can argue about it.

So my question is a patient who's 38 years old gets this treatment. He goes into complete remission for a year or two. He's going to live, hopefully, for X decades. What's the chance that he's going to relapse and quietly develop high-grade dysplasia and carcinoma?

DR. DONNER: I think to answer that question in a confirmatory manner would require the proposed extension to 5 years follow-up that Axcan is on the record of supporting. I'm not sure how definitive we can be with the 2-year follow-up. The 5-year data will be much more convincing of that.

DR. KELSEN: So I'll take from that that we can draw no long-term conclusions beyond 2 years at this point.

DR. MARTIN: We have analyzed results with regard to a time window of 2 years, which is usual for people to get a feel for the efficacy of a treatment. As said, several patients are on ongoing in the trial. The median observation time is 3.5 years to date, and we are prolonging our observation for 2 to 3 more years. Of course, at 2 years, those are the results, but they are at this moment highly statistically significant.

Does that erase all risk of some patients undergoing reappearance of the high-grade dysplasia? Well, at least we will know from our trial, and this is, by all means, the largest controlled study, prospective, multicenter, that has been ever conducted, including a therapeutic arm and also a surveillance of patients. The ones receiving only omeprazole are, more or less, under a surveillance protocol. Although it was not meant to be a surveillance protocol.

DR. KELSEN: Let me have an oncology question to the gastroenterologists because I don't know. If somebody has PDT, the esophagus is preserved. The reason they got it because they have GERD, so they presumably still have GERD. So the organ is still at risk. Would you not expect them to re-epithelialize with Barrett's or does

this ablation presumably remove that possibility?

DR. WOLFE: I think the study is early on, but this study itself and others have shown that you don't ablate every single patient. Not only that, with sampling error, you have to assume that they either still may have it or that it can reappear. There's also data I know of from another study that, using a monoclonal antibody, was actually able to find Barrett's high-grade dysplasia that wasn't seen by the pathologist.

This is an evolving area. This is not the end. This is the beginning, and you'll see more and more of this, other techniques, other methods to diagnose. For example, stains weren't done with methylene blue to look for areas of Barrett's in these patients, I don't think. There are techniques being done endoscopically, for example, microscopic endoscopy. They will look much more carefully.

So my view as a gastroenterologist is that if they receive phototherapy, they still need to be surveyed. I'm not sure. I'd welcome other people's opinions. Michael, do you agree? Bob?

DR. CAMILLERI: I think Dr. Overholt and Dr. Wang are probably much more expert than myself, and we could ask them their opinion.

DR. OVERHOLT: I'm not sure I'm answering the

right question, but I would like to comment on the patient who has had the esophagectomy. A number of patients in our series in our center have had previous esophagectomies, particularly distal, and they all reflux and they reflux severely. Many of them will recur with redevelopment of new Barrett's and new dysplasia. By the way, for those patients, the alternative therapy is not an additional esophagectomy. The surgeons won't do that. So we have to treat those patients with PDT and then follow them. And they will continue to recur 2 or 3 years down the road and we retreat them. So esophagectomy is a cure, but it's not without its problems of recurrence also.

Now, the other question that I'm not sure I'm addressing?

DR. WOLFE: The question was you give PDT to the patients, look down there. The pathologists now are going to have extra work to do because they'll be reviewing all the cases all over the country, and they can't find any evidence of high-grade dysplasia. Is the person cured and say goodbye and never see you again? Or does that person still have possibly occult high-grade dysplasia and requires further surveillance?

DR. OVERHOLT: They definitely will continue to require surveillance. Once they are clear, however -- that is, clear of dysplasia and clear of Barrett's -- and their

squamous epithelium re-epithelialize and you have proven that by biopsies on two exams, you can extend your surveillance endoscopy to 1 year. There will be some new data published in a couple weeks on long-term results and it's very clear that they need to be followed up long-term.

DR. MARTIN: For patients that have received therapy, namely PDT, if the Barrett's esophagus is still present, there is a standard of care that is recommended by the American College of Gastroenterology guidelines that calls for surveillance more so if the patient has had or has high-grade dysplasia or low-grade dysplasia or only Barrett's. There are guidelines for that. So patients should be investigated as standard of care under the ACG guidelines. So I don't think it will be any different after they have received PDT or esophagectomy.

And all the difficulties we're recognizing at present concerning the risk of missing high-grade regression in a shorter period, et cetera, apply to the disease not so much to the treatment. So this is the same situation for a patient. If you miss reappearance of high-grade dysplasia, this patient would need a therapeutic intervention, be it esophagectomy or any other form. The advantage with our therapy is that you can repeat it, whilst you cannot replace an esophagus that is missing.

DR. WOLFE: Dr. Mangel, then Ms. Cohen, then

Dr. Gillett.

DR. MANGEL: I have a question which has two or three parts. I'll ask the entire question to give you the flavor of where I'm going, and please feel free to answer it in any manner you like.

I couldn't quite tell from either the briefing document or your presentation -- I would like a little more information on the inclusion criteria of exactly who the patients were. The title of your NDA, I gather from your briefing document, indicates for those who are not considered candidates for esophagectomy. Your proposed indication gives me a different connotation, for those who refused esophagectomy. I actually view those as distinct populations, especially when I hear that the patients are otherwise healthy.

I want to ask the entire question at once to give you a flavor of where I'm going.

I also do not note in either your briefing document or in the presentation any mention of dropouts during the study, although in the FDA briefing document, a very high dropout rate in particular in the omeprazole group is mentioned. And if I'm correct, only 11 patients finished the 2-year treatment while you also have a substantial but smaller dropout rate in your active treatment group.

My suspicion -- but I was wondering if you could comment on it -- the data presented on your slide 70, which is your summary of clinical response, as well as your cancer rate, for me last observation carried forward analysis is of actually little value in endpoints such as what you're looking at here, in particular for cancer rates. And my suspicion is if you were to look at the number of patients at any point in time, your actual differential between your active treatment and your omeprazole only group would be larger than what you're actually presenting here, but by the same token, the absolute rate of progression to cancer in your active group or the incidence of cancer in your active group would be greater.

I don't know if that's too --

(Laughter.)

DR. MARTIN: You should have informed me to take notes of your question. I'm sorry. Which question would you prefer to be answered first in the sequence of --

DR. MANGEL: Whichever you would prefer. So to summarize, exactly who the patients were. My impression, a very high dropout rate. My impression, the data are represented as the total ITT population using a LOCF imputation scheme rather than an observed population, particularly for your clinical response and your cancer

incidence.

DR. MARTIN: Dr. Donner, do you want to address one of the questions?

DR. DONNER: The ITT analysis, the intention to treat analysis, included all patients randomized to treatment whether or not they discontinued therapy. You are correct that the discontinuation of the therapy, if anything, would only dilute the observed treatment effect.

Although the results in general of the study are highly significant, both clinically and statistically, I think it's always important to do a number of analyses to ensure that the conclusions hold up under many different assumptions. So analyses were also done on an efficacy basis, including evaluable patients. They were done including and excluding certain sites. Multiple logistic regression analyses were also done controlling for baseline factors. And no matter how one analyzed the data, the conclusions remained highly significant.

DR. MANGEL: Could you comment on when you looked at your observed population, what was the cancer rate versus using the denominator of your ITT population?

DR. MARTIN: I don't really get the question.

DR. MANGEL: That's fine. Maybe I'll reword it.

DR. MARTIN: I could come back to some other

questions and then --

DR. MANGEL: No, but that's okay. I could reword it. My understanding from reading the FDA briefing document is, for instance, in your omeprazole only arm, only 11 of the 70 patients completed the study. 20 of those patients dropped out because they developed adenocarcinoma during the course of the study. My understanding, once again from reading the FDA briefing document, is of the original 138 patients, you only had 81 completers in your active treatment arm with 18 percent of those withdrawing because of cancer. I guess, first would be if you agree with those numbers.

Second would be to me the percent of patients which developed cancer in each of the two arms. When you look at a completion, including those who withdrew because of cancer, in your denominator, the percentages are higher than indicated. Yet the differential between your active and your placebo group is greater in favor of your active group.

DR. MARTIN: I expect that you remember that this is a 2 to 1 randomization. Could that have introduced a bias in your evaluation of things?

DR. MANGEL: No.

DR. MARTIN: No? Okay.

We have a slide which tells about the dropouts.

It's a bad name, but discontinuation of therapy which lists the patients that discontinued therapy in both groups. You have figures here. In the omeprazole group, 49 patients discontinued therapy. 20 of them -- those are absolute numbers -- progressed to cancer, and 21 underwent other therapy and 6 discontinued therapy for administrative reasons.

I suppose that you are questioning the number of patients who progressed to cancer in the omeprazole group whilst there was a 2 to 1 randomization. So there were fewer numbers as compared to the ones progressing to cancer in the PDT group, which is 18. Of course, percentages are different there.

DR. MANGEL: No. I'm sorry. I apologize because I know I'm not being clear. That's not the essence of the question.

DR. SHIH: I don't usually do this, but perhaps I can help out a little bit here. There is a difference between drop out of a therapy and drop out of a study. I think your question is they used the ITT approach. If I interpret this correctly, let me know. Nobody dropped out of the study. They are discontinuing from the therapy. However, they are followed up still. Am I right?

DR. MARTIN: Yes. Except for 6 patients that are not there for administrative reasons, dead persons, and

adverse event, the others are still in the trial.

DR. MANGEL: But, for instance, in the placebo group, 21 of the individuals went on to other therapies for treatment of their high-grade dysplasia.

DR. SHIH: Correct. That's why I say this is ITT. They don't drop out from the study. Whether they had an AE or treatment failure or they had another therapy intervention, they are still counted in the originally randomized group which only can jack up the rate for the control group. So that's why I think this is a more conservative approach here that they took.

I think you're right. You're asking the question, suppose you do an evaluable patient approach and what would be the result, and they can present that for themselves.

But I tried to help out to explain there is a difference between your concern of discontinuation of the therapy or discontinuation from the study. But I think they all followed up by the end of the study. Is that correct?

DR. DONNER: Yes.

DR. BRAWLEY: And if I can jump in -- I apologize for jumping in front of Ms. Cohen. I understand your point, Dr. Mangel, but it actually speaks in favor of the therapy.

DR. MANGEL: No, I agree. I think it will enhance the differential between the active arm and the placebo arm. I thank Dr. Shih because that was actually the clarification that I needed. What wasn't clear to me is with the large percent of dropouts, that their surveillance was continuing. So if a new cancer developed, it actually would have been counted as a cancer.

DR. BRAWLEY: They really weren't dropouts. They were discontinuance of therapy.

DR. MANGEL: That's an important clarification. Thank you.

But if you could answer then the very first. I assume that these were candidates for esophagectomy, just individuals who opted not for esophagectomy.

DR. MARTIN: I think you're right. In the consent form, as any gastroenterologist, more so involving a strict protocol like the one we had, we had to give the patients all the therapeutic options available to them at the time of enrollment. That included obviously esophagectomy or other non-approved therapy or even surveillance. So when the patient gave consent to this trial, they have probably by default refused esophagectomy, which was offered to them as a therapeutic option.

So we are, as you just said, very conservative in the label of our proposed indication when we say, in

patients refusing esophagectomy. Conservative we are. We think that there is currently a standard therapy for progressing high-grade dysplasia or even in situ cancer. The patient should be submitted to esophagectomy. So we respect that as the clinical standard care, but this is alternative therapy, which of course takes the patient away from a surgical resection and offers them the possibility of repeated treatment under a standard of care follow-up afterward.

And in view of the robustness of our data, we think that perhaps we should remove this limitation to patients who refuse esophagectomy for patients being in general good health, hopefully that patients that are submitted to severe therapy or strict therapy, esophagectomy or something else, that they are in a good, healthy condition to at least support and sustain the therapeutic intervention.

DR. WOLFE: Before you go any further, again, Ms. Cohen knows this. It's much more efficient for the discussion to finish the question of one of the panel members, even if it requires going in front of the next person because it just makes for a much better flow of the discussion rather than coming back and repeating that.

Dr. Houn, did you want to make a comment about this also?

DR. HOUN: Yes. I just want to jump on what Dr. Camilleri and Dr. Mangel are asking about, the study population, the control group being omeprazole with surveillance, and whether you think the data support the therapy as an alternative to surveillance versus what I think the sponsor is asking you to suggest as an alternative to esophagectomy. So I think that's a discussion point they're asking for some assistance by the committee to help discuss.

DR. WOLFE: We'll go on again for more questions related specifically to the presentation. Ms. Cohen.

MS. COHEN: Some of this you will have to repeat. I'm curious to know again how often people had to receive second treatments and how soon after.

DR. MARTIN: By protocol patients were not allowed to receive a second course of therapy before 3 months. But we have numbers on that if we can prompt the slide, and I'll ask Dr. Overholt to come and discuss that.

DR. OVERHOLT: While we're searching for the slide, there was a limitation in the clinical trial for the length of the Barrett's that we could treat. We could treat up to 7 centimeters of Barrett's. Some of these patients had long segments, 10 or 12 centimeters, and therefore would naturally require a second treatment. Some

had more difficult-to-treat Barrett's esophagus with dysplasia and required a second treatment. But all felt that they wanted that second treatment compared to the esophagectomy because they ended up with organ preservation and were happy to be able to live that way.

MS. COHEN: Apropos of that, I don't know if this is a clinically correct question or not, but one takes an antibiotic. You start to have an improvement. With people who start to take this treatment and they progress to cancer during this treatment -- do I understand that while they're being treated, they do progress to cancer?

DR. OVERHOLT: Some patients who received the treatment only did go on to progression to cancer, 13 percent; 28 percent in the control.

DR. WOLFE: The treatment was received and then they were followed.

MS. COHEN: No, but what I guess I'm trying to think in my mind, if this had any therapeutic value as they went along in the treatment or you develop cancer even if you do get the treatment. And apropos of that, how many people developed cancer after they had the treatment? I have here 15 percent. I don't know if I wrote that correctly or not.

DR. OVERHOLT: 13.

DR. MARTIN: The 15 percent is the difference

in number of cases observed and percentage in the omeprazole group, no treatment, versus the percentage of patients who have progressed to cancer in the PDT group. This difference of 15 percent, the one Dr. Camilleri alluded to, is I thought a good reflection of the absolute risk reduction of progression to cancer, and this can even lead to analyze it or present data in number of needed treatments to prevent one cancer. So if you treat 7 patients, you can prevent 1 cancer. In medical therapy, such good data confers this therapy a very high rate. This is my opinion, of course.

MS. COHEN: Let me finish one more quickly. I want to complement them, first of all, on their presentation, and I also want to thank Dr. Levine because that was a very sensitive thing that you raised and it's of grave concern to all of us.

On the photosensitivity, how many of your patients did or did not follow directions? Because it seems like it's rather important.

DR. MARTIN: Well, it's difficult to say. Most patients had mild photosensitivity which is inherent in this use of the drug, a photosensitizer, that is diffused in the body and goes into replicating cell groups. That includes the skin and photosensitization comes after that. But 69 percent were mild events, and they were diagnosed

as sunburn.

We don't have control of what patients are doing after therapy and after they have been suggested to stay away from external light or even internal light for some time.

So we are even considering -- and we've already implemented -- information to patients. When patients go to receive Photofrin therapy in centers that deliver this therapy, they are shown a video which pounds into them all the good suggestions to stay away from external light. But how many and how much compliance do they put into the suggestion, well, I guess it's normal life. I cannot say any more than that.

DR. WOLFE: I want to add to that. These patients are sedated, and if you tell them, a lot of times they'll forget you ever told them that. So before we let any patient go after endoscopy, they have someone with them so another person who can remind that they cannot go out in the sun because of photosensitivity reactions. We have these kind of treatments. We tell patients a lot of things. We can't go home with them and hold their hands for two days. So this is actually pretty low.

DR. MARTIN: Mr. Chairman, Dr. Wang would like to make some comment.

DR. WANG: I think Ms. Cohen has raised a very

important point because this is a toxicity that isn't common. It's not like what people expect to deal with. And we do spend a lot of time in our treatment centers trying to educate patients. We always have them see the video, see a nurse, and I talk to them before they receive the treatment, before they receive the injection, many days before. And despite this, you've got to remember, this is a population of older males, and you know how well they listen.

(Laughter.)

DR. WANG: It's a big problem. Really what happens is they try to get away with it by not following the directions for a little bit, and then if they get a slight sunburn, then they know you're serious because they really don't know what to expect. And that's what I've noticed is the behavior of our patients. They really want to just test it a little bit and they go, whoops, he wasn't kidding, and then they stop.

MS. COHEN: Then it begs the question, why is it 85 percent males and 99 percent caucasians? Why wasn't there a more mixed population?

DR. WANG: That's the epidemiology of the disease. Unfortunately, as you notice, most of these are male patients. It's at least an 8 to 2 predominance of males, and they're virtually all caucasians.

MS. COHEN: That makes me feel better since I have GERD.

DR. SHIH: Excuse me.

DR. WOLFE: Dr. Gillett was next actually. Do you want to comment on this?

DR. SHIH: Well, continue with the patient population discussion. I was wondering if you can show us the distribution of how many patients you enrolled in each center.

DR. MARTIN: Yes. We have this slide, and I say up front that in Dr. Overholt's center, 25 percent of the study population were included and enrolled in his center. We did subanalysis to make sure that there was no site imbalance because of that. I can give you the outcome of this subanalysis, and there are no differences in the primary efficacy as well as in safety. But I guess we will prompt those data and someone will review them.

DR. LEVINE: I think more important, I think what he's asking is like what were the least number of patients enrolled, 1, 2, 3, 5 at one center versus 20. If we can get some idea of that, we'd know how representative it is or whether there were mainly just 3 or 4 centers contributing of the 30 centers.

DR. MARTIN: That was not the case, but I don't remember all the figures for all the centers.

DR. WOLFE: Just real briefly, how many of the centers had more than 5 patients?

DR. MARTIN: Oh, more than half of them if not more, 75 percent.

DR. WOLFE: How many had more than 10 patients?

DR. MARTIN: I don't have that by heart at this moment.

DR. WOLFE: This was presented at DDW, wasn't it?

DR. MARTIN: Yes.

DR. WOLFE: There was a good sampling. I saw the presentation. There were many patients at many centers. It's truly multicenter with a lot of patients in each one.

DR. MARTIN: The overall clinical response without site 07, just to clear the 25 percent enrollment in Dr. Overholt's center. That does not answer all your questions, but the difference was not significantly different than the whole group including this subgroup. We can prepare that during the break.

DR. WOLFE: That would be better.

DR. MARTIN: Yes, because I don't have that in mind at this moment.

DR. WOLFE: How many people have questions?

(A show of hands.)

DR. WOLFE: There are several. So we really should take a break right now and come back and finish the questions. So it is 10:55. We will come back here at exactly 11:10.

(Recess.)

DR. WOLFE: We'll reconvene. We'll continue with questions for the sponsor.

DR. MARTIN: While people are coming back to their seats, could you prompt the slide on the distribution of patients by center? And I'll ask a colleague of mine, Dr. Patrick Colin, who is Vice President, Clinical Research at Axcan, to explain this slide. Please, Patrick.

DR. COLIN: Thank you, Francois.

So as we can see, we have two slides describing the exact number of screened as well as randomized patients in the PHO BAR 01 study. As we can see here, we have the first column describing the number of patients screened, the second column on the right describing the number of patients randomized in the study. As previously mentioned, Dr. Gene Overholt's site was the site where the highest number of patients were both treated and randomized. And then it's not in the order of numbers, but we can see that only a few sites had more, let's say, than 10 patients randomized. There are 14 here, another 14, 51 at Dr. Overholt's site, 13, but most of the other sites had less

than 10 patients randomized.

The same observation can be made on the next slide. Here we can see the number of randomized patients ranges between 3, 2, 7. Then we have another 13 sites here. So basically we have less than 5 sites where there were more than 10 patients randomized and all the other remaining sites where there were less than 10 patients randomized.

DR. MARTIN: Does that answer part of the question?

DR. WOLFE: It answers the question. We looked at how many sites there were and how many had more than 1 patient. For me it's fine. Does anybody have any other questions regarding different sites?

(No response.)

DR. WOLFE: Let's move on. Dr. Gillett, you had some questions, and then we'll entertain more questions from the panel.

DR. GILLETT: Yes. The first question has to do with the extent of involvement of other drugs, supplements, diet, whatever and the intra-arm variation. Was there any use of NSAIDs, aspirin, cox-2 inhibitors by any participants in the study? If so, was it different from one arm to the other?

DR. MARTIN: A good question. I think to give

you the formal answer on it, we'll see if we have backup information. Would you like to comment on that?

DR. COLIN: So this is basically a listing of concomitant medications that were taken by the randomized patients throughout the PHO BAR 01 study. It's organized or classified according to the therapeutic category. For example, here you have nervous system, drugs acting on the nervous system. You have dermatological drugs and so on.

Then you can see two columns. The first one on the left is the patients who were randomized in the Photofrin PDT plus omeprazole treatment arm, the number of patients who took some of these medications, as well as their percentage. Then on the right side, the omeprazole only treatment arm with the same statistics, absolute number of patients taking some of these medications and the respective percentages.

DR. GILLETT: But those don't display very accurately the use of the drugs I asked about.

DR. WOLFE: Specifically, you want to know about NSAIDs, whether they're selective or non-selective.

DR. GILLETT: Right.

DR. COLIN: Of course, in this table, we don't have this very detailed information, but that's something we could get from our data listing, of course.

DR. WOLFE: Well, if you look at

musculoskeletal, which I think would probably encompass NSAIDs, they're 37 percent.

DR. GILLETT: A lot of people are on aspirin for their cardiovascular --

DR. COLIN: In this category, what we can see is that the relative percentage of patients taking this kind of medication was comparable between the two treatment arms.

DR. GILLETT: And also to return to previous -- I think it was slide 84. What fraction of the people receiving multiple dilations had received multiple treatments? What was the multiple treatment role in the multiple dilations? Because it's the multiple dilations I hear about most frequently as being the ones that are problematic where there's a tear in the esophagus or something can go wrong, and the more treatments you have, the more chance there is for mischief.

DR. MARTIN: You're asking if repeat treatment with PDT has an influence on the incidence and severity of strictures. Is this what you're asking?

DR. GILLETT: Yes.

DR. MARTIN: Dr. Overholt will comment on that.

DR. OVERHOLT: The incidence of stricture formation was 8 percent if the patients received one -- I'm sorry. Let me restate that. 36 percent of our patients do

have esophageal strictures. Of that percentage, 8 percent had received one treatment; an additional 22 percent, two treatments; and an additional 5 percent had received three. So multiple treatments is clearly a risk factor in developing an esophageal stricture, and it's because of that overlap phenomenon.

Now, anybody with an esophageal stricture -- you can't tell who is going to get the severe one and who's going to get the mild one. There's no way to predict. I don't know that there's any association of multiple treatments in severe strictures.

DR. GILLETT: To finish up, do you notice any difference between patients -- you have the drug regimen. Do you have any difference between patients in terms of their diet, dietary supplements, or other alternative therapies that they may or may not tell you about? Do you have any sense of their compliance? For example, I didn't do well with omeprazole. I know other people who switched to other PPIs or H-2s. How do you know that they're complying with that?

DR. MARTIN: Well, I think by protocol patients had to be compliant with the protocol. Of course, if the patient is not taking the medication at home, again we're not there to check all the time. And what they don't tell us about whatever specific diet or regimens or natural

products or whatever, we can never know. So I think it's inherent in any clinical trial that there are some missing information that are not there. But your question is well taken. I don't think we can pull out any data or numbers to satisfy your interrogation here.

DR. WOLFE: Dr. Brawley.

DR. BRAWLEY: Yes. Can we pull up the slide about people who were lost to follow-up and discontinued therapy again? I just want to go through it and make sure that I understand some key points.

While we're waiting for that, on slide 61, which we can just look at in our packet, am I correct in assuming that there is a relative risk reduction of about 50 percent in terms of HGD in people who got Photofrin versus people who got the omeprazole in the observation arm?

DR. MARTIN: I think it's more than that.

DR. BRAWLEY: More than 50 percent.

DR. MARTIN: 73 percent in the PDT group versus 40 percent in the omeprazole group, and the duration or the maintenance of this elimination of high-grade dysplasia is much shorter in the omeprazole group alone versus the PDT treatment.

Am I responding well to your question?

DR. BRAWLEY: I think so. I'm going to need

the statisticians to help me. I think that's about a 50 percent relative reduction.

The slide that was just up here. I'm sorry. It was the slide that looked at all the discontinuance that we were talking about when Dr. Mangel had his questions.

DR. MARTIN: 32.

DR. BRAWLEY: Yes. When I look at the progression to cancer, I see 13 percent in the treatment arm and 28 percent in the omeprazole arm. I am wondering is it appropriate to say that over -- this is 2-year follow-up data. Correct?

DR. MARTIN: Yes.

DR. BRAWLEY: Is it appropriate to say that there's a greater than 50 percent decrease in the progression to cancer on the treatment arm with PDT plus OM versus OM? The period prevalence of esophageal cancer is more than halved on the Photofrin arm.

DR. MARTIN: Dr. Donner, would you concur with this evaluation of those numbers?

DR. DONNER: Yes, that would be true.

DR. BRAWLEY: I come from a world of cancer epidemiology and giving tamoxifen to women for 5 years or finasteride to men for 7 years in hope of a 25 percent reduction in relative risk of disease. So that's a significant finding to me.

DR. WOLFE: Dr. Carpenter.

DR. CARPENTER: In that same line, a 15 percent absolute reduction in the risk of getting cancer at any time in any prevention study would be absolutely enormous. The absolute reduction with tamoxifen to prevent breast cancer is on the order of 10 percent, to give you an order of magnitude.

DR. WOLFE: Dr. Kelsen.

DR. KELSEN: Following up the oncologic line, you may have given us this, but I'm not sure I got it. Do you have the stage of the cancers at the time they were found? I noticed the survival curves are close to 100 percent. So that implies to me that the cancers that were found in a third of the patients in the omeprazole arm and the 15 percent in the PDT arm were at a very, very early stage. So I'd like to see that.

And secondly, it means that this is one of the first large-scale prospective trials that would say that surveillance allows you to find cancer at an early stage even if it's in the omeprazole arm. This is the largest prospective study for that, isn't it?

DR. WOLFE: There are other data, but this is the largest. We know that surveillance is very important in these patients, and what they're showing is surveillance is important even after therapy.

DR. KELSEN: Yes. There has been some controversy about patient selection, but this is a pretty big database.

DR. WOLFE: Actually there has been discussion -- it's really interesting -- regarding this. One of the fellows of mine presented at our grand rounds, and people were trying to minimize the importance of Barrett's in general, saying it's not that important. It doesn't really progress. You can watch these patients. Don't worry about it because the chances of getting cancer isn't really 1 percent per year as it is in the largest series of the meta-analysis published in 1997. It's only 1 in 250.

So I stopped there. These are physicians. I said to people who aren't physicians in the audience, do you like your chance of being 1 in 250 getting cancer every year and then in 10 years it's 1 in 25? That's not too bad, is it? You don't mind that very much.

(Laughter.)

DR. WOLFE: And I think that sometimes we forget as physicians what the patient is actually feeling. That is a very high percentage and to say don't worry about it is very easy for us to say because we're not the patient.

Dr. Camilleri?

DR. MARTIN: Doctor, in answer to your

question, this is the cancer staging at the time of discovery in the PDT/OM cancer group, the treated group, and I think we have it on the other group. So as you see, they are very, very early stages. There's at least one good reason for that I think, that the patients are surveyed every 3 months by protocol.

DR. WOLFE: Any other questions, comments?

(No response.)

DR. WOLFE: That's great. We'll move on then, and Dr. Kaminskas will now give a presentation on behalf of the FDA.

DR. KAMINSKAS: Mr. Chairman, committee members, ladies and gentlemen, good morning. My name is Edward Kaminskas. I'm the medical reviewer for this new drug application for Photofrin. Dr. Milton Fan is the statistical reviewer.

The sponsor has presented a very comprehensive overview of the data supporting the new indication, and I shall limit myself to several topics and present some analysis from a little different point of view. I shall talk about study design and treatment, study endpoints, selection of patients again, course of patients during the study period, and some safety aspects.

Dr. Wang and Dr. Overholt described the reasons for treating high-grade dysplasia in Barrett's esophagus.

I have no disagreement with their statements. However, I would like to just remind the audience about the public health impact of Barrett's and of adenocarcinoma of the esophagus so that we don't lose track of what we're talking about. That is, most patients with adenocarcinoma of the esophagus, 94 to 98 percent, do not have a history of Barrett's. Most patients with Barrett's esophagus do not develop cancer, as Dr. Wolfe mentioned, an annual incidence of half a percent or less. Risk of adenocarcinoma in an older patient with gastroesophageal reflux disease is very low, 6,500 cases per year among 10 million GERD patients.

However, the only known premalignant lesion for adenocarcinoma is high-grade dysplasia. And that requires medical management and poses a challenge of medical management. As mentioned before, there's wide disagreement on how to manage high-grade dysplasia, from watchful waiting until there's a sign of localized adenocarcinoma, to ablation of high-grade dysplasia to reduce the risk of adenocarcinoma, to esophagectomy. Each approach has its champions.

The original new indication for Photofrin is as stated above: ablation of high-grade dysplasia in Barrett's esophagus among patients who are not considered to be candidates for esophagectomy. The revised new indication is as stated below: ablation of high-grade

dysplasia in Barrett's esophagus among patients who refuse esophagectomy and who are in overall good health. I'm not going to comment on this issue, and perhaps the committee will. I assume that the revised indication is as a result of the study and thinking about what actually happened because there were a lot of patients who had esophagectomy in both treatment arms. So they could not have been preselected for this trial if the indication was as stated originally.

You've heard this before. PHO BAR 01, multicenter, randomized, two-arm trial with a minimum of 24 months follow-up. Patients randomized, a 2 to 1 ratio. 138 patients to Photofrin PDT and omeprazole; 70 to omeprazole only.

And the two supporting studies from the Thompson Cancer Survival Center, single center, open-label trial, minimum 12-month follow-up. All of the patients treated in the same way as they were in the PHO BAR 01. The follow-up is 12 months, however. So I think the data we have to look at in a little bit different way.

As noted in the first trial, 93-07, patients were randomized to two light doses. In 96-01, after that first trial with its high incidence of esophageal strictures, Dr. Overholt attempted a tapering schedule of steroids immediately after the light therapy to see whether

there would be any effect. Unfortunately, the results were negative.

However, we have that experience so that I have to bring to the members' attention that Dr. Overholt contributed a total of about 45 percent of all the patients studied in these three trials. A remarkable achievement.

In those two supportive trials, there were 168 patients and 86 of them were with high-grade dysplasia.

Esophagectomy is no ball as Dr. Wang said, and as a surgeon said to someone I know very closely, your life will never again be the same. Well, I would say that Photofrin photodynamic therapy is not as arduous but it's not simple and it's not for everyone, not for all comers.

You heard this before that patients could have had up to three courses, and this slide just simply illustrates how many patients in PHO BAR 01 had how many courses. There was supposed to be an interval of 3 months, at least, between courses so that you could see that if a patient had three courses, that took a good part of the year at best and in some cases longer because the intervals were longer. There were two reasons. The main reason was the extent of high-grade dysplasia. The length of the balloon light delivery system, the maximum was 7 centimeters, and half of the patients in the study had areas of esophagus affected by high-grade dysplasia that

were longer than that. That means automatically you had another course. And if it was even longer than that, you had a third course.

So here you are, multiple courses. You start out with 130. You received your Photofrin which doesn't make you glow in the dark, but it makes you glow in the light.

(Laughter.)

DR. KAMINSKAS: You have a pretreatment of nodules, followed by the balloon light. And then 2 days later, there was another session for some of the patients, treatment of skip areas. You wait 3 months and there you are again. You go through the same thing.

Now, it's clear that you don't want to overlap areas and increase the risk of strictures, but you don't want to also leave areas that are untreated because that defeats the treatment. So from my reading of this protocol, this requires a lot of expertise and a lot of training, and I admire the people who do it.

The complete ablation of high-grade dysplasia is the primary endpoint at 24 months' follow-up with replacement with normal squamous epithelium, CR1; with some metaplasia, CR2; or with some low-grade dysplasia, CR3.

Here are the secondary endpoints. The way they're specified, I have to say many of these secondary

endpoints could not be achieved because it required 50 percent of patients reaching an endpoint, and within 2 years there was no time for progression to cancer. In fact, a lot of these -- let's say, for example, duration of response. You see the Kaplan-Meier curves, and as far as I'm concerned, when I come to 24 months or 730 days afterwards, I don't know what I'm dealing with because the denominator gets to be smaller and smaller. So 50 percent of 2 people is 1 person. It recalls to mind Mark Twain and what he had to say about statistics.

(Laughter.)

DR. KAMINSKAS: But I couldn't have done this without Dr. Wang either I have to say.

Now, at the beginning of this PHO BAR 01 pivotal trial, the agency's concern was the primary response variable must reflect an improvement in long-term clinical outcome. Histopathological effect might be a surrogate endpoint for measuring clinical benefit, but it doesn't prove it. If we could live with high-grade dysplasia forever, no one would have a treatment for it. There's no reason to treat it except for one reason and that is the risk of developing an adenocarcinoma. At that point, the agency and the sponsor agreed that the follow-up time of 5 years or more is recommended, but the follow-up of at least 2 to 3 years is acceptable for the submission.

The efficacy results as noted before, 82 percent of patients treated -- this is the evaluable population. These are people who actually received treatment. 82 percent in Photofrin compared to 39 percent in the omeprazole only arm. In the Thompson Cancer Survival studies, 94 percent, all excellent responses. I have to say the only surprise in this slide for me is the 39 percent response rate for patients on omeprazole only, and we'll come to that.

What about these responses as defined before? This is in percentages. What you see is that the Photofrin photodynamic therapy group had mainly CR1, complete replacement with normal epithelium, and the omeprazole only, most of them had, of course, no response. And the second one are CR3 responses which means low-grade dysplasia and definite dysplasia, very rare CR1s or CR2s.

So the question is, does this therapy actually reduce the risk of developing cancer? This is directly from the sponsor's study, and as noted by Dr. Brawley just now, in the Photofrin group, 18, or 14 percent, progressed to cancer of those treated. 29 in the omeprazole only. It's twice as many. And the 12-month data from the Thompson Cancer Survival Center is not inconsistent.

Now, I have to say that 24-month data is really very important data because if it takes you a year before

you finish treatment, for those patients you basically have 12 months of follow-up. Up to then, you're being treated. So we wanted to look at these people who progressed to cancer. We wanted to see who progressed to cancer and whether we can learn from these failures something about the success of this therapy.

So who progressed to cancer? If you had a Photofrin photodynamic therapy treatment and you had a complete response of any kind, you had a chance of 6 percent, 6 out of 106, of developing cancer over the next 2 years. If you had Photofrin therapy and had no response, you had about a 10-fold higher chance of developing cancer. 12 out of 24, 6 out of 106. Big difference. So what happens is that a responder has a very good chance and a nonresponder has a very poor chance of staying cancer-free.

Now, in the omeprazole only arm, almost everyone, 19 out of 20 patients failed to respond. Only 1 patient responded. So if you have a response, it makes a big difference whether you're going to develop cancer or not during this period of follow-up.

Now, as I mentioned before, of course, the photodynamic therapy group had mainly CR1 responses. Of those who progressed to cancer, they had poor quality responses. They had low-grade dysplasias or indefinite dysplasias or they didn't have a response at all. There

was not a single CR1 response who progressed to cancer.

In the omeprazole only group, there was only 1 responder who progressed to cancer and had a poor quality response, a CR3. So I don't know. It could be that in between all those metaplastic areas and dysplastic areas, there was a little bit of high-grade dysplasia hidden as well.

So to us, this was very gratifying to take your data and learn something from it.

I'm going to come back because everyone talked about it up to now, selection of appropriate patients. I think Dr. Bronner, everyone up to now has referred to this, the nonconfirmation of high-grade dysplasia diagnosis of 49 percent. Whatever we decide to do with Photofrin and photodynamic therapy, this is a primary issue because if you don't have it, you don't need this treatment.

There was one other thing that I wanted to mention before I come to this point, and that is when the sponsored analyzed their data, what were good predictors of complete response? One of them was 3 months or more treatment with omeprazole. High p value, like .022, .05, whatever. Significant. Which brings to mind that patients who responded in the omeprazole only arm may not have been treated with omeprazole before, and it sort of makes you think that perhaps before this diagnosis is really firmed

up, people should have their acid reflux treated.

Patient disposition. It sends a message here. After 2 to 3.5 years of follow-up, there was 61 percent of patients in the Photofrin photodynamic therapy group, 81 out of 138 intent-to-treat population, who were continuing on and will be continued on for the next 2 to 3 years. But look what happened to omeprazole only patients. 84 percent dropped out. There were only 16 percent remaining.

Well, this is the surveillance arm, and if I look at this, I would say the surveillance arm did not work very well in this trial. If 84 percent leave, you don't have much of a follow-up in 5 years. For example, looking at days when people left the trial, it was clear that in the photodynamic therapy group people left in bunches, and you could see that they had their quarterly esophagoscopy and suddenly they were discovered to have high-grade dysplasia, and boom, they went on to other therapy. The people on omeprazole left sort of one by one, quarter by quarter by quarter. And I'll come to a point here, but I just wanted you to remember that surveillance in this group does not work even though the literature says this is a good option for some.

And I would say that there are some people that have wide differences as to how they want to be treated. There are some people who got this treatment at age 88 and

you would think at age 88 surveillance would not be such a bad choice, but they are treated. I have enough patients of 100 and above who say, do something, Doctor. I don't want to be in the surveillance group.

(Laughter.)

DR. KAMINSKAS: Other therapies. Now, the two main reasons for dropouts were either because people developed cancer or they were treated with other therapies other than the assigned therapy. Of course, you see here that 14 percent of patients in the Photofrin group had other therapies for high-grade dysplasia. In omeprazole, it was more, 32 percent, and similar data in the Thompson Cancer Survival Center, 20 percent.

Dr. Overholt was going to show you -- and I'm not sure that he did -- as to what kind of therapies people elected. They're in the slides in the packet. I don't think he showed them. I would just want to point out that in the omeprazole only arm, about three-quarters of them chose to have Photofrin PDT. Of course, those who failed Photofrin went on to have esophagectomy and all kinds of other ablative therapy, not Photofrin. Some of them had had four courses of Photofrin and that made them the exception.

Next I would like to relate to safety issues. The way I understand it, of course, you can take adverse

events. You can split them up into 139 symptoms and you can figure out if somebody had a myocardial infarction because they're all coded under different little adverse events. The way I read this is that there were acute events related to the light treatment. After all, what happens is you get Photofrin. They become very photosensitive and you shine a light on their high-grade dysplasia and they slough their esophagus, at least they slough the mucosa. That's the point of the treatment. So you have a bare exposed wound in the bottom of the esophagus.

Now, 100 percent of patients did not have these acute events. I don't know why but they didn't. About half of them did. They had chest pain. They had abdominal pain. They had fever. They had nausea. They had vomiting. They couldn't swallow. It was painful to swallow. And all of that is the acute injury as if you sloughed somebody's esophagus. That's what you'd find. And it takes a few weeks for that esophagus to heal and those symptoms go away. This is not chronic. This is acute.

You have skin photosensitivity, and I have to say reading over the sponsor's literature cautioning about skin photosensitivity is really enlightening because we don't think about it. We're so tied into ultraviolet light

sensitivity, that we don't think that there's any other kind. Yes, it is like a sunburn, but it's not caused by the sun, ultraviolet light. It's caused by visible light.

So, for example, it was very interesting to see sitting in dentists' offices. If you have a dental light shining on you, you're going to come out with a burn. You may lose a tooth, but you'll have a burn to boot. Or going to out-patient surgery to have some stitches put in or whatever. All of those lights are your poison, and people are really very, very well cautioned about it.

If I remember right, I think in the principal trial, PHO BAR 01, there was a higher percentage of skin photosensitivity than there was in the Thompson Cancer Survival Center because I think Dr. Overholt and his colleagues have been doing this now for some number of years, and they've had every experience that's to be had. So they warned their patients.

The caution is 30 days, but some people go up to 90 days. So it's a tricky issue. But it doesn't last. It goes away even if you have a burn and it's not many who do.

And finally, I wanted to touch on subacute events related to healing and these are the esophageal strictures which is esophageal narrowing on endoscopy. These are not adverse events. You'd get different

percentages if you look at the adverse event data. This is on esophagoscopy. The gastroenterologist sees esophageal narrowing that required dilation. The patient cannot swallow solid food.

I have here the three trials and I have them in order of when they were completed. In the first trial, 99 patients, 93-07, 42 percent of patients had strictures. That's when Dr. Overholt decided we have to do something about them and the next trial tried the steroid therapy. 36 percent had strictures. This is the entire safety population. This is not high-grade dysplasia. This includes all comers. This is adenocarcinoma of the esophagus. This is low-grade dysplasia, indefinite dysplasia, everyone. In the PHO BAR 01 trial, 36 percent, for a total of 38 percent.

So we don't know how to deal with it as of now. I know that people are working on it, but right now the only one is esophageal dilation or in French it's bouginage I think, isn't it, if I remember right? And you pass bougie.

This is not to minimize it. This data has been presented and this is for number of patients with dilations in all the trials, all three trials. Number of patients with dilations, 121. This is I think the PHO BAR 01 study data was presented. This is for all the studies.

Statistics remain very much the same. 50 percent had more than 10 dilations. There was an occasional patient who had dilation due to high-grade dysplasia in the esophagus. They had one dilation and they were fine. In the omeprazole only arm, if somebody needed to be dilated, one dilation is fine. This is complex and this was not minimized by the presenters.

So I come to my summary. Aggressive surveillance. At least in PHO BAR 01, this was not a good option. Patients are modern Americans. For the most part, they want treatment. Do something, Doctor.

Information on the risk of cancer in high-grade dysplasia is essential for evaluation of treatment options. I don't know if we'll ever have it. We don't know if high-grade dysplasia regresses to low-grade dysplasia. Just like low-grade dysplasia, we don't know whether it will regress to completely normal epithelium. We don't know the rate of progression of cancer. We don't know so much about this entity, and yet we may not be able to learn as shown by this trial. It's going to be difficult to enroll people in a surveillance trial.

Esophagectomy. We have no information. Once patients had esophagectomy, they were disenrolled. We don't know what happened to them for the most part. There was one person in Britain who died following post-surgical

complications for esophagectomy. This trial does not provide us information. We have to look at the surgical literature.

Photofrin photodynamic therapy. Relatively well tolerated. There were very few patients who withdrew because of adverse events. This is a key indicator for all drug trials, how many withdrew because of adverse events. Very few.

There were no deaths either due to treatment or because patients developed metastatic esophageal cancers and died.

Most serious adverse events were gastrointestinal and dehydration.

Strictures were troublesome, manageable.

2-year follow-up suggests that Photofrin PDT is effective. Patients had 50 percent lower cancer rate. Complete response rates were twice as high as in the omeprazole group. Complete response was associated with a lower risk of cancer than non-response. Mainly highly quality CR1. That is normal epithelization. After the therapy, only patients with CR3 progressed to cancer.

But a 2-year follow-up is too short to demonstrate effectiveness in reducing the long-term risk of cancer. We don't know that. We don't know the rate of recurrence of high-grade dysplasia in patients who have had

a complete response. We don't know the rate of high-grade dysplasia progression to cancer. And we're going to be awaiting results of the PHO BAR 02, which is in process, and it may tell us something about it and certainly will give us a little more confidence. So that's the reason why the sponsor is not asking for this indication because we just don't know enough at this point, the long-term risk of cancer.

Thank you very much for your attention.

DR. WOLFE: Thank you.

It's noon. We have time for questions, but again, I do want to limit the questions specifically to Dr. Kaminskas' presentation. Other questions can follow.

The public forum will be extremely short. As a matter of fact, right now there will be no public forum because there's nobody here to speak, but there may be someone coming forward.

So we do have some time, again, for questions for this specific presentation regarding the FDA evaluation. Any questions? Dr. Camilleri.

DR. CAMILLERI: That was a very nice summary. Thank you.

I want to ask the same question that I asked before. Do we have any idea of the factors that predispose to lack of response? That's the first question.

And the second question, while I agree with Dr. Brawley that there is a 50 percent reduction in cancer risk, I would like to reiterate that the appropriate control group is a total esophagectomy. We have to keep that in mind.

DR. KAMINSKAS: I have no disagreement with either point.

The first part, both the sponsor and I in my review looked for risk factors for failure to respond. We couldn't come up with any. Originally, it was thought to be age. So, for example, the division was over 65/less than 65. A favorite number since Chancellor Bismarck's 65 division line. So we said if that is the case, is there an age at which this therapy is contraindicated? Because there were people up to age 88 being treated with it. So then the sponsor provided an analysis by decade, and an analysis by decade didn't show anything.

Smoking has nothing to do with it. Drinking doesn't have anything to do with it. We couldn't come up with risk factors that would predict response or failure to respond.

The only issue that I have that I pointed out is this issue of 39 percent response rate in patients who are treated with omeprazole for 3 months. Now, that gives you some food for thought, but in terms of the Photofrin

group, we couldn't come up with anything.

DR. WOLFE: I actually mentioned that before, and that really is the most surprising data to me as well. You don't get that kind of response. They're a surveillance group being treated.

Actually I have a question very specifically that is related to that peripherally. Were these patients given specific instructions how to take omeprazole? Were they told to take it before breakfast and before dinner?

DR. WANG: Yes.

DR. WOLFE: The reason I bring that up is because statistically based on our study, 30 percent of those patients before they came into this study were taking their medication before bedtime. We've published this. People are not given proper instruction and take the medication incorrectly which has a great impact on how these PPIs work.

So then the question now comes to the pathologist. How many of these patients initially had inflammation which may cause architectural distortion and possibly some issues with regard to true diagnosis of high-grade dysplasia. Again, I'm not a pathologist. You are but I know from other GI pathologists there is some concern if there is inflammation present. For example, I don't biopsy anybody looking for Barrett's unless I know

inflammation is gone endoscopically.

I think these are important issues because that is a very surprising result, to get that kind of response with a PPI alone.

DR. BRONNER: We very carefully tracked the issue of inflammation and particularly whether we as pathologists thought it was obscuring the diagnosis. So there are a series of boxes that we had to check off for each biopsy and each slide. One of the categories was inflammation, yes or no; ulcer, yes or no; and if ulcer, can high-grade dysplasia be excluded. If you look at that category, those cases that had a yes answer, there was disagreement among the pathologists. So we know when we can't tell. So that information was tracked.

However, there was no difference between the omeprazole only and then the PDT arm in terms of this obscuring inflammatory problem.

DR. WOLFE: No, but they all got omeprazole across the board.

DR. BRONNER: Yes. Everybody got omeprazole.

DR. WOLFE: So you would expect that. The question is, I guess, was there a higher rate in the patients with omeprazole only who went on to regress who had inflammation or ulceration on the initial biopsy?

DR. BRONNER: I can't answer that question off

the top of my head. I suspect that it has to do with the extent of high-grade dysplasia and that the ones that appear to be responding have a small amount and therefore we've got a bigger effect of sampling error.

DR. SHIH: Mr. Chairman, can I follow up that question?

DR. WOLFE: Yes.

DR. SHIH: Now, the 39 percent you asked that question -- and earlier I commented on that they used the ITT approach for the 39 percent. I believe that when they do the evaluable, it's only 1 patient difference. So it's 39 percent whether you do ITT or you do the evaluable.

But there are hidden things here that I'd like to clarify from the sponsor. You have 21 patients from the control group, the omeprazole group, who discontinued surveillance and went to another therapeutic intervention. If a patient discontinued the surveillance and went to the other intervention, then later had a response -- I don't know how many cases there are. This is part of my question -- would you count that as part of your 39 percent?

DR. KAMINSKAS: You mean people who had another intervention?

DR. SHIH: Well, you see, your definition of CR1 plus CR2 plus CR3 is that anytime during this follow-up time, if you have a response, then that's counted here for

the 27. Now, how many out of the 27 was after this group, after a patient has chosen another intervention?

DR. KAMINSKAS: Once a patient chooses another intervention, they're dismissed from the trial. They're discontinued.

DR. SHIH: No, I don't think so because your denominator for the study of 9 percent is 70 or 69. As I said, there's only 1 difference. But the total remaining at the end of the follow-up is 11 patients. So I don't think so. I think that your denominator is for the patients randomized. So you must have counted some of the patients in the 27 who went to another therapy.

This is part of the reason I suspect why the 39 percent was high, and the other reason could be this, that the FDA statistician actually did a very nice job here that gives you another calculation of consistent responders. In other words, it's not anytime that during the endoscopy monitoring you have a response, then you count it as 27. Suppose you have to maintain the responders for other times, and then that figure here I have is only 1 patient. Only 1 patient out of 70, which is only 1.4 percent, have a consistent response. So there's a difference between 39 percent and 1 percent here. Because the definition of a consistent responder or any one time during this time, you can have one shot and then you've called it a response.

That's a big difference there.

DR. KAMINSKAS: No. I went through the sponsor's data on consistency. In other words, I was afraid of exactly what you're saying, and that is, that a person would respond one time and would become a responder and then doesn't respond any more times. In other words, they do quarterly biopsies and at one time they show a response and then they stop showing any response. So I was really afraid. But actually they were, to my going over these data, pretty consistent responders until they failed, and when they failed, then they failed and had intervening therapy or whatever it is.

But I'm sorry that I'm not quite getting your answer. Say, for example, if somebody fails the omeprazole arm and has Photofrin treatment, that patient is discontinued from the trial, is not counted in the Photofrin group or in the omeprazole group. It's counted as a failure. So maybe I'm just not getting your question.

DR. SHIH: I disagree.

DR. KAMINSKAS: What do you mean you disagree?

DR. SHIH: Well, first of all, I'm trying to explain why you have observed 39 percent response rate in the omeprazole group. It's very high, as the chairman said. There are two reasons that I suspect.

One I confirmed here, which is the consistent

responders question. Consistent responders, you only have 1 patient according to Dr. Milton Fan's calculation here by the FDA. And if you redefine your responders by consistent responders, then you only have 1 patient. Okay, that's one.

DR. WOLFE: That would make sense. Dr. Bronner has explained that too, and we talked about the sampling error is very, very pronounced in these patients.

DR. SHIH: Right.

And then the other reason is -- it's only a suspicion here -- that because your denominator is 70 in the ITT patient population, and then the definition of ITT is that you follow up, as I asked earlier to clarify that -- you follow up everyone. Now, suppose you have one shot of the biopsy which is after you have switched to intervention. Then you called it a responder. The ITT definition is that you attribute that responder to where you randomized which is omeprazole group only. And I asked clarification if there are cases like that.

DR. KAMINSKAS: I have to tell you that we got data listings by patient number from the sponsor, and I went over every single patient who was enrolled in the trial and who responded to what.

We'll have Dr. Fan explain because I'm not capable of doing it.

(Laughter.)

DR. FAN: My name is Milton Fan, statistical reviewer.

When I reviewed the submission, I found out that they have some problem because the defined response is only visit have response, is considered response. And I'm thinking the more restrictive way is look at every visit is considered response. And also it is considered they have three kind of responses, CR1, CR2 or better, or CR3 or better. The more restrictive is CR1, so (unknown words) the data has come out. 11 patients for Photofrin have a response, CR1, for all visits. For omeprazole only 1 patient have a response and the difference is about a 7 percent difference. It's a slight numerical benefit, but does not achieve statistical significance.

DR. WOLFE: Dr. Carpenter.

DR. CARPENTER: One thing which would help to clarify this would be to know if the patients who went to alternative therapy are then censored after that so they can no longer be added back into the response group.

DR. KAMINSKAS: Yes, they were.

DR. WOLFE: Dr. Kelsen.

DR. KELSEN: I think when the sponsor showed us the slides of patients who developed cancer in the treatment state, they also had what treatment they got, and

a number of patients in the omeprazole group I think did not come to esophagectomy. They were treated with PDT for these early stage cancers.

So I have a question and an observation. My question is, was there a central pathology review of the diagnosis of malignancy?

DR. KAMINSKAS: Yes, of course. Of course, those quarterly biopsies all went to Seattle, University of Washington.

DR. KELSEN: Fine. So cancer is clearly cancer.

And I think that your analysis then of risk on the basis of response is a very interesting analysis, also sort of an alarming analysis because I imagine there are people who don't get screened. So here you have a screened group getting omeprazole, and if they don't have a good response, they have a real high risk of getting cancer if they really have high-grade dysplasia. It makes you wonder about all the people who are not being screened who have high-grade dysplasia.

DR. WOLFE: You got it and it's one of the problems that was brought up. Dr. Levine mentioned there's a serious shortage of gastroenterologists and people are taking medication because it works. They feel better, but one thing that wasn't mentioned is that how you feel has

nothing to do with how your mucosa looks. There's a complete disconnect. And it's one of the dangers of people taking medication without supervision, without some kind of -- I hate to use the word "supervision." It sounds too authoritarian.

DR. GILLETT: Surveillance.

DR. WOLFE: Surveillance.

Any more questions?

DR. KELSEN: Can I just make one more brief comment?

DR. WOLFE: Sure. I'm sorry.

DR. KELSEN: From a public health point of view, that's a very significant observation, and as a medical oncologist who does GI, I can tell you our clinics are quite full with patients who eventually develop upper GI cancers, so it may complete your loop.

DR. WOLFE: Keep in mind that when Dr. Wang presented his data about the increase in this disease in all western countries, this has occurred during a time when we have the most potent acid suppression available to us. So would it be greater without? There are a lot of questions still unanswered.

Dr. Levine.

DR. LEVINE: I'm sure this is not in the purview of the agency, but it's almost like off-label. Did

your group look -- obviously in the questions that you want us to consider this afternoon, you looked at the expertise and the professionalism of various individuals, educational aspects, and aspects of who is going to do this and how it's going to be labeled and restricted. My question to you is, has the agency been concerned about the possibility of careful restriction in this, and do you have something more to say about this before we talk about it this afternoon about restriction in the use of Photofrin therapy by who, for who, et cetera?

DR. KAMINSKAS: Well, in the original submission, there was an indicator that the sponsor looked at as to whether expertise with this therapy produces better results. And they defined it if people who had 10 patients or more -- I don't remember the exact definition -- would they be getting better results than patients like Dr. Overholt who has hundreds of them. And it turned out that they didn't. So I was kind of leery about whether that's going to become an issue as to who is going to get it.

However, the present proposed label by the sponsor says, this therapy should be administered only by physicians with special training. Now, we have not had in the agency discussions about this point yet, but we will during this coming month.

DR. WOLFE: I actually wanted to mention that. I want to discuss this this afternoon under 1(b) and I want to add a 1(c). That was a specific question. I really want to discuss this this afternoon as one of the questions that we'll be discussing among ourselves to make recommendations.

Dr. Carpenter.

DR. CARPENTER: Perhaps for this afternoon, but a similar issue. The proposed new indication is for people who are in overall good health, and yet clinically people who are not in good health and are extremely high risk from esophagectomy might be a target group for this. Was that proposed by the sponsor or was that arrived at in discussion with the agency? Or where did this new indication come from?

DR. KAMINSKAS: It came from the sponsor.

DR. WOLFE: I'd like to discuss that because I had the same question. People generally refusing surgery or not having surgery are those who can't tolerate surgery. So I think we should discuss that as well under 1(d).

Any other questions regarding this presentation? If not -- oh, I'm sorry. We have one more. Dr. Gillett.

DR. GILLETT: Just a brief question. There are maybe a dozen different kinds of esophageal cancer that

develop, but only one is associated with Barrett's? Only one?

DR. WOLFE: I'll answer that unless the pathologists want to. The most common cancer of the past of the esophagus was squamous cell of the esophagus which is interestingly disappearing. It's getting lower and lower and lower. It's being replaced by adenocarcinoma of the esophagus in the setting of Barrett's. So Barrett's, reflux is associated with adeno. Squamous has other risk factors which I won't get into.

This is a fascinating area in general, but this is the FDA not the NIH. Why this is happening is a question for us to all think about. I raised one of the issues. This is occurring at a time when we have the best therapy ever available. Why is this continuing to rise? There are a lot of theories, but no proof, and one of the reasons is there's no good animal model.

It is now 12:23. The members of the panel have a place reserved in the restaurant for lunch. We will reconvene at exactly 1:25. Enjoy your lunch.

(Whereupon, at 12:23 p.m., the committee was recessed, to reconvene at 1:25 p.m., this same day.)

AFTERNOON SESSION

(1:35 p.m.)

DR. WOLFE: We're past the time for reconvening and it is our fault. Actually it's the restaurant's fault for not providing us our checks, but we need to get started.

At this point I'd like to call upon Dr. Justice to read the questions for us and again to explain to us what our charge is this afternoon.

I'm sorry. Before we get started, is there anybody in the public who wants to speak in the throngs out there?

(No response.)

DR. WOLFE: No, okay.

Dr. Justice.

DR. JUSTICE: The first question concerns the appropriate patients for Photofrin PDT. Part (a) is the diagnosis of high-grade dysplasia was confirmed by the central reference laboratory in about 50 percent of patients with that diagnosis. We'd like you to discuss what impact the inability to confirm a high-grade dysplasia diagnosis has on the use of Photofrin and ask for your recommendations to ensure use of this therapy in the appropriate population.

Part (b) of the question is, should the

diagnosis of high-grade dysplasia be confirmed by a reference laboratory of acknowledged experts before Photofrin PDT is undertaken?

The second question concerns efficacy. Part (a) is, do the applicant's data demonstrate efficacy of Photofrin PDT in complete ablation of high-grade dysplasia in Barrett's esophagus?

Part (b). Is a 2-year follow-up period adequate to demonstrate cancer risk reduction in high-grade dysplasia patients treated with Photofrin PDT?

And part (c) is, how frequently should patients who have undergone Photofrin PDT be monitored by esophagoscopy?

Part 3 is, is the safety profile of Photofrin PDT acceptable?

Question 4 concerns follow-up. The applicant is continuing to collect follow-up data in the PHO BAR 02 study for an additional 3 years. PHO BAR 01 and PHO BAR 02 taken together will provide a maximum of 5 years of follow-up for patients in the two arms of the study. Is this adequate to demonstrate cancer risk reduction in high-grade dysplasia patients?

And I think that's it.

DR. WOLFE: Thank you.

1(a) and 1(b) are actually very closely tied

together because if we look at (b) first, if we all feel that there should be a central laboratory, it sort of answers your question for (a). Would that be correct?

DR. JUSTICE: That's correct.

DR. WOLFE: So how about we'll go a little out of order. We're going to go to -- since we discussed this at great length this morning, let's just go and discuss 1(b). The way I'd like to do this is the same way as yesterday. If you weren't here yesterday, I'm not going to explain it to you. No, actually I will. We'll go around the room and you have a chance with these kind of questions to give your opinion, and then we will actually just get a hand vote on this.

So I'd like to go in different orders. We'll start with Dr. Goldstein. This is 1(b). Do you feel a central reference laboratory should be used to make the diagnosis of high-grade dysplasia before the PDT is used?

DR. GOLDSTEIN: I should remind the chair that I don't have a vote.

DR. WOLFE: But we have a discussion, though, and we're not going to vote right now.

DR. GOLDSTEIN: Thank you.

I feel that the diagnosis is -- on the basis of the evidence I've seen here today, I think a central reference laboratory would be useful.

DR. WOLFE: Dr. Mangel.

DR. MANGEL: I'm sure I'll be in the minority opinion on this. I would say no, and the logic would be we don't do that now for esophagectomy. The decision tree where we are when a biopsy comes back is now two arms. You do surveillance or you do esophagectomy. Nothing is different. It's just that we have now a potential new treatment algorithm instead of esophagectomy for the same biopsy reading to do PDT. I don't actually see any difference, and I would say no to that.

DR. WOLFE: Dr. Kelsen.

DR. KELSEN: I would sort of take the middle ground. I would say that you don't need one laboratory with a panel of acknowledged experts. I would think that you would want to say something about having a pathologist with expertise in this area should declare that it is a high-grade tumor.

DR. WOLFE: Ms. Cohen?

MS. COHEN: I would say yes, hoping that in any part of the country there is some reference place where you can go to get the adequate information.

DR. WOLFE: Dr. Gillett?

DR. GILLETT: I'm going to agree with Allan about the lack of a need to do this simply because we're having to move ahead.

DR. WOLFE: I'm just going to make one point. I agree with your point, but two wrongs don't make a right. I think what the surgeons should now do is reconsider their thoughts, and if they're over-diagnosing, they should go back and consider a central reference laboratory. That's not our charge here. So I think rather than repeat what I consider an error, I would favor a reference or reference laboratories to make this diagnosis or further diagnosis.

Dr. Levine.

DR. LEVINE: With my concern, which I'll raise again, about unnecessary use in performing dilatations as a complication of Photofrin therapy and with Photofrin therapy being utilized, if it happens to be a potential money-maker for gastroenterologists, the story goes back anecdotally to many other issues. And you can look at the capsule endoscopy which in our regional area, it's a minimal $15,000 procedure, not paid by the insurance initially but subsequently paid, a very small amount, by insurance. There's nobody interested in the area that wants to do this. Currently the academic center, our own center, does this.

I think with Photofrin therapy it would be extremely important to limit both to expertise and also expertise opinion. Therefore, I think it's mandatory to have a regional or multiple laboratories with expertise to

review the slides.

DR. WOLFE: Dr. Brawley.

DR. BRAWLEY: I would prefer the statement that the slides should be reviewed by someone experienced in diagnosis of the disease. I don't think it should be mandatory however.

DR. WOLFE: Dr. Shih.

DR. SHIH: My answer is simple. Yes, you need a reference laboratory to confirm the high-grade dysplasia.

DR. WOLFE: Dr. Carpenter.

DR. CARPENTER: I would favor a statement similar to Dr. Brawley's, that the slide should certainly be reviewed by a pathologist with expertise in the area.

DR. WOLFE: Dr. Camilleri.

DR. CAMILLERI: I agree. Pathologists with expertise.

DR. WOLFE: Any other comments? I'll make just one comment about leaving it vague with expertise. Who will make that decision? That's the only question that remains. If there is some sort of panel who is considered to have expertise, that makes it a little easier. But does anybody else want to comment on that?

DR. LEVINE: A brief comment.

DR. WOLFE: Yes, Bob.

DR. LEVINE: In our own area, to give you an

example, we cover about 2 million people in Syracuse, New York, as the academic center from Binghamton up to Canada and over to Rochester and Albany. It's frequent that we get referrals from other pathologists to our pathology department and sometimes we don't, and we see errors all the time in diagnosis in gastrointestinal pathology. I think it depends on your area. If you're talking about large centers, certainly it's going to be easy to have good GI pathologists expert in that area. In other areas, there simply aren't any, and I think it's a problem. Whether it's an expert who's been trained well or a central laboratory, I think that's beside the point, but we need expertise.

DR. WOLFE: Dr. Kelsen.

DR. KELSEN: Would FDA accept the statement being amended to read reference laboratories, or does the question have to be a single reference laboratory?

DR. WOLFE: I was going to actually just leave it to them. Let's have the question rephrased, laboratory or laboratories, and we'll let you make that decision.

DR. BRAWLEY: Who determines what is a reference laboratory?

DR. HOUN: In this situation it would probably be, if this is a recommendation and we would agree with it, that we'd work out with the company whether it's training

programs they do and then the labs have gone under these training programs or they show that they have these particular types of expertise. But I think you could interpret the question either laboratory or laboratories.

DR. WOLFE: Any more discussion, questions?

(No response.)

DR. WOLFE: So we'll vote now, those who are voting members. The question will read the following. Should the diagnosis of high-grade dysplasia be confirmed by a reference laboratory or laboratories of acknowledged experts before Photofrin PDT is undertaken?

All in favor of requiring the diagnosis be confirmed, raise your hand please.

(A show of hands.)

MR. PEREZ: Can we go around?

DR. WOLFE: Do you want to go around the room? Never mind. We'll go around the room for the record. Dr. Mangel, yes or no.

DR. MANGEL: No.

DR. WOLFE: Dr. Kelsen?

DR. KELSEN: Yes.

DR. WOLFE: Ms. Cohen.

MS. COHEN: Yes.

DR. WOLFE: Dr. Gillett.

DR. GILLETT: No.

DR. WOLFE: Wolfe is yes.

Dr. Levine?

DR. LEVINE: Yes.

DR. WOLFE: Dr. Brawley?

DR. BRAWLEY: No.

DR. WOLFE: Dr. Shih?

DR. SHIH: Yes.

DR. WOLFE: Dr. Carpenter?

DR. CARPENTER: Yes.

DR. WOLFE: Dr. Camilleri?

DR. CAMILLERI: Yes.

DR. WOLFE: The final vote is 7 yeses, 3 noes.

So you don't need (a). Right?

DR. JUSTICE: Right. You've answered the question.

DR. WOLFE: Dr. Carpenter.

DR. CARPENTER: Can I presume that the ultimate recommendation may be some mixture of reference laboratories or expertise or something in that area?

DR. WOLFE: The FDA knows our feeling and I think they'll take it from there.

I want to add another question here that we discussed before, and let's make it 1(c). Should there be some sort of certification for gastroenterologists performing this procedure? Keep in mind that the sponsor

did look at this question and found that there was very little difference among the centers who had considerable expertise with those who didn't. Actually just a quick question, a nod yes or no. My take on this from just doing other procedures there's a very sharp learning curve here, a very steep learning curve. Is that correct?

(Off microphone speaker.)

DR. WOLFE: It's not steep? That means very quickly. That's steep. Not flat. It's steep. So it means very quickly.

DR. HOUN: You need to speak into the mike.

DR. WANG: Yes, it's fairly easy to learn. The only thing you have to do is put down the fiber and light. Management of the patients afterwards takes some time, but that's general medical care.

DR. WOLFE: Well, that will be discussed how we take care of them afterwards. Can I assume that the sponsor will be producing some kind of learning materials for those who will be undertaking this procedure? Okay.

I guess we can go on then. Is that okay? Is that good enough for you, or do you want a vote? We should vote on that.

DR. HOUN: Go on, yes.

DR. WOLFE: Just go on? We'll go on.

Question number 2(a). Do the applicant's data

demonstrate efficacy of Photofrin PDT in complete ablation of high-grade dysplasia in Barrett's esophagus? Again, that's complete ablation of high-grade dysplasia in Barrett's esophagus.

We'll start this time with Dr. Camilleri.

DR. CAMILLERI: Not satisfactorily in a large enough number of patients for me to say yes. So I say no.

DR. WOLFE: Dr. Carpenter.

DR. CARPENTER: It was complete eradication in 55 percent. So I think the answer is yes to a limited extent.

DR. WOLFE: I'm sorry. Complete would be a CR3?

DR. CARPENTER: Yes, but I'm talking about the CR1's. That's complete eradication.

DR. WOLFE: The question is complete ablation which we're assuming that means there is no dysplasia left at all.

DR. MARTIN: If I read, "in complete ablation of high-grade dysplasia." Isn't it what is written there? That's the question. And that was the primary efficacy endpoint of our study.

DR. WOLFE: Again, give us those figures on that. High-grade dysplasia was --

DR. MARTIN: 77 percent.

DR. WOLFE: 77 percent, okay.

Let's start over again then. Dr. Camilleri, 77 percent ablation rate.

DR. HOUN: Let's just have the sponsor define the 77 percent and the 39 percent because there was some confusion on what is the numerator and denominator derived.

DR. WOLFE: Can the sponsor actually put up a slide to show that?

DR. MARTIN: We have a slide up and Dr. Donner will comment on it.

DR. DONNER: The 39 percent and the 77 percent refer, respectively, out of the groups randomized to the control and to the experimental group who are known to have responded at 24 months.

We have another analysis, if we put that up, which only looks at those people who were biopsied every 3 months for 2 years who never did discontinue therapy for any reason. In this case the proportion of responders compared in the two groups is even more favorable to PDT. 89 percent versus 39 percent. It's a coincidence that the 39 percent in this graph is the same 39 percent figure that we saw in slide 61. But the 89 percent response rate is even higher among those that were biopsied every 3 months.

So this just suggests that any bias resulting from that analysis that was done first was in the

conservative direction, and I also believe it's supported by the time to progression of cancer results which don't deal with this issue at all because the Kaplan-Meier curves incorporate censoring.

DR. MANGEL: Dr. Donner, am I correct? When I look at that, it looks like the patients who developed cancer in the active treatment group are removed from the denominator, when I see the number 88.

DR. DONNER: No. These are the people in the denominator who were biopsied continually every 3 months for 2 years.

DR. MANGEL: I understand that. So if an individual developed cancer, they're removed from the denominator.

DR. DONNER: Yes, for this particular analysis, they would have to be because you couldn't biopsy them after that.

DR. MANGEL: Yes. And so that might at one level be overestimating the response rates, I would agree, for people who drop out for other reasons, but for individuals who are withdrawn from surveillance because they developed cancer, I believe they should remain in the denominator.

DR. WOLFE: Can we see the ITT data?

DR. DONNER: This is not an ITT analysis.

DR. WOLFE: You have the ITT analysis, though. You have that.

DR. DONNER: Yes.

DR. WOLFE: Could we just see that? Would that answer your question, Dr. Mangel?

DR. MANGEL: No. I believe it was answered, that the patients are not included.

DR. WOLFE: But do you want to see the ITT data? Do you want to see it?

DR. MANGEL: No. I think it's fine. It would just add 18 to the denominator for the active group and about 20 to the denominator for the control group.

DR. WOLFE: Any more questions or clarification? Dr. Camilleri.

DR. CAMILLERI: The clarification is that in fact, with due respect to whoever put this question together, I think that even though this may have been the primary endpoint of the study, from a clinical perspective it leaves the patients with the risk of occurrence of high-grade dysplasia. And we need to come back to that.

DR. WOLFE: We'll come back to that. I think Dr. Justice had that in mind when (b) and (c) were set up as questions.

So let's just stick with this question right now. Did the therapy work, at least in the short term?

We'll start over again. Dr. Camilleri.

DR. CAMILLERI: So to answer that specific question, the answer is yes.

DR. WOLFE: Dr. Carpenter?

DR. CARPENTER: Yes.

DR. WOLFE: Dr. Shih.

DR. SHIH: Yes.

DR. WOLFE: Dr. Brawley?

DR. BRAWLEY: Yes.

DR. WOLFE: Dr. Levine?

DR. LEVINE: Yes.

DR. WOLFE: I say yes.

Dr. Gillett.

DR. GILLETT: Yes.

DR. WOLFE: Ms. Cohen.

MS. COHEN: I have a question because I don't understand it. Does it mean they're never going to have it again?

DR. WOLFE: No. That's (b) and (c). We'll get there in a second. Did it work in the short term?

MS. COHEN: Well, it doesn't say short term.

DR. WOLFE: No, but (b) and (c) imply that.

MS. COHEN: Well, I have problems with the question, so I'm going to abstain.

DR. WOLFE: Okay.

Dr. Kelsen.

DR. KELSEN: Yes.

DR. WOLFE: Dr. Mangel.

DR. MANGEL: Yes.

DR. WOLFE: So we have 9 yeses and 1 abstention.

Let's move to 2(b). Is a 2-year follow-up period adequate to demonstrate cancer risk reduction in high-grade dysplasia patients treated with Photofrin PDT?

Let's start this side. Dr. Goldstein, this won't be a vote, but I want to hear your opinion.

DR. GOLDSTEIN: I think it is barely adequate, but the company has already committed to a longer follow-up and I think that should be more than adequate.

DR. WOLFE: Dr. Mangel.

DR. MANGEL: I agree with Dr. Goldstein that the 2-year period demonstrates a risk reduction but in itself is not adequate.

DR. WOLFE: Dr. Kelsen.

DR. KELSEN: I think they've demonstrated a delayed time to progression. I don't know if we know overall progression would be delayed, and the model I would think about is where we have therapies in cancer where we try for organ preservation for as long as we can. So in that sense, yes, they've answered it for 2 years. I don't

know what it will be for 5.

DR. WOLFE: Ms. Cohen, is 2 years sufficient?

MS. COHEN: As long as there's a follow-up after 2 years.

DR. WOLFE: Then you're saying no, it's not sufficient.

MS. COHEN: I'm concerned. Yes.

DR. WOLFE: So you're saying it's not sufficient.

Dr. Gillett.

DR. GILLETT: Yes, I agree that it's sufficient.

DR. WOLFE: I don't think it's long enough.

Dr. Levine.

DR. LEVINE: I don't think it's long enough. I'd like to see a post-marketing 5-year follow-up as proposed by the group.

DR. WOLFE: Dr. Brawley.

DR. BRAWLEY: I am familiar with several drugs that have been approved by the FDA because they reduce the period prevalence of a disease. Tamoxifen is approved for taking it because it reduces one's risk of breast cancer during the period in which one is taking the drug, not after one stops taking the drug. As such, I think that they have demonstrated that you reduce the 2-year period

prevalence of esophageal cancer.

DR. WOLFE: I don't think that's the question that's being asked. Most of us are saying, yes, it did work for 2 years, but I think the question is stop there, goodbye, see you in another lifetime, or do we talk about these patients need to be monitored further.

DR. BRAWLEY: Oh, it becomes a very easy question then. No one has figured out if it reduces the risk at 3 years. That scientific question may have been addressed by treating the people for 2 years, but no one has shown us 3- or 4-year data, so that's an easy question to answer.

DR. WOLFE: So keeping that in mind, do you say goodbye at 2 years or do you continue on with surveillance after that?

DR. BRAWLEY: Continue surveillance.

DR. MANGEL: Dr. Wolfe, I'm sorry. I actually read the question differently than what you're describing.

DR. WOLFE: What you need to do is look at the progression of questions, and that's the reason I said -- unless I'm wrong.

DR. HOUN: The issue here is a claim for cancer risk reduction versus indicated for ablation of high-grade dysplasia. Help us with that.

DR. BRAWLEY: Let me go back again. What I

think they have demonstrated is a cancer risk reduction in the first 2 years. Have they demonstrated a cancer risk reduction over a period of 5 years or for the remaining life of the patient? I don't know any procedure -- has polypectomy risen to that level? No, I don't think so. Has ablation of cervical dysplasia risen to that level? I don't think so.

DR. WOLFE: As long as you bring up colon polyps --

(Laughter.)

DR. WOLFE: As long as you're bringing it up, the reality is this. The colon and esophagus are very, very similar in how they behave. If you look at progression of inflammation, it goes to inflammation, metaplasia, dysplasia, high-grade dysplasia, invasive cancer. Exact same. As a matter of fact, the antibodies that actually pick up Barrett's esophagus have a colonic epitope. So they're very similar organs in that regard. Ask any gastroenterologist. You would have an adenoma. Guess what we do in 5 years? We check again to see if you have a metachronous lesion. So recurrence does occur. So if you're going to have that, then you're saying 2 years -- maybe we showed a 2-year risk reduction here, but we have not shown anything beyond 2 years.

DR. BRAWLEY: I don't want to prolong this, but

I think we're saying the same thing. I'm saying I see a benefit for the first 2 years, but you've got to follow up after that.

DR. WOLFE: So you're saying 2 years is not -- okay, fine.

DR. SHIH: I think we need to follow up longer than 2 years. I really want you to understand the definition of follow-up, surveillance. That is a potential problem in this study. The design says continue endoscopic surveillance every 3 months, or 6 months if four consecutive quarterly HGD negative follow-up endoscopic biopsy result. However, I heard and I also saw the graph presented, and actually it wasn't followed that way. So the follow-up really has to be reinforced.

DR. WOLFE: Dr. Carpenter.

DR. CARPENTER: I think they've shown a 2-year risk reduction. I'm sure that 2 years is not long enough to know the efficacy.

DR. WOLFE: Dr. Camilleri.

DR. CAMILLERI: No.

DR. WOLFE: Now, I'm going to divide this question in two for the FDA to answer your question. I'm going to try first to see if we can do it by a raise of hands. Has a risk reduction for 2 years been demonstrated in this study? Let's show by hands first. If not, we'll

do a roll call. Again, the question is has the sponsor shown a risk reduction over a 2-year period by use of Photofrin. If you think so, raise your hand.

(A show of hands.)

DR. WOLFE: How many do not think it's been demonstrated?

(A show of hands.)

DR. WOLFE: 9 to 1 that a 2-year risk reduction has been shown.

Now, in follow-up to that question, how many of you feel 2 years is an adequate period of time to say that's it, you're cured? How many think that it is an adequate period of time? Adequate. How many think it is adequate, it is sufficient to say the patient is cured? Do you any of you feel that way?

DR. HOUN: We're not interested in that answer.

(Laughter.)

DR. WOLFE: I am.

DR. HOUN: Okay.

DR. WOLFE: It flows to the next question.

DR. HOUN: We're interested in they've done the 2-year study. You've seen the data. Can they get a claim for cancer risk reduction?

DR. WOLFE: We just said that.

DR. HOUN: Okay.

DR. WOLFE: For 2 years only.
DR. HOUN: For 2 years only.
DR. WOLFE: That's all that's been demonstrated is 2 years at this point.
DR. HOUN: So you're saying, unlike tamoxifen, which doesn't say reduce your risk of breast cancer while you're on the drug --
DR. WOLFE: This is not a drug. This is a --
DR. BRAWLEY: It says reduce the period prevalence.
DR. HOUN: What are you saying you're advising us? To say that the claim would be reduces your risk of cancer for 2 years. Is that what you're saying?
DR. WOLFE: I think that's what the data shows. This is different from taking a drug. Don't the oncologists generally call 5 years disease-free pretty much cured?
DR. KELSEN: I think the issue they're dealing with -- yes, an established esophageal cancer that's been resected that hasn't recurred within -- actually the highest is the first 3 years, but after 5 years is highly unlikely to recur. And that's why that period.
I don't know if you're looking at it in this way or if you can, but again, the standard of care would be esophagectomy, we established this morning. And this would

be for at least 2 years they reduce the time to the development of a tumor and preserve the organ in the patients for that period. And I think what we're wrestling with is we don't know if cancer will then occur in that organ without esophagectomy 4 years down the line or 5 years down the line.

DR. BRAWLEY: Dr. Houn, what I would advocate would be a very literal, almost skeletal like statement that says at 2 years after starting therapy, the rate of esophageal cancer was lower in the treated group versus the group that got the other therapy.

DR. WOLFE: Ms. Cohen.

MS. COHEN: Cancer did develop in some people after they have the treatment. So I say using FTC language, which I'm more comfortable with, there is a strong possibility that it does reduce, but to say it does, period, I think puts everybody in a very vulnerable position.

DR. WOLFE: Does the sponsor feel they've demonstrated anything beyond 2 years? We're talking about 2 years. So they're going to do other studies to see if it goes beyond that. How can they claim something that hasn't been investigated?

Dr. Mangel.

DR. MANGEL: To me -- and I think I understand

Dr. Houn's point -- there is a difference between saying that sentence in the clinical trials portion of the label versus making a claim that this reduces -- or whatever the wording -- you know, this reduces the prevalence or frequency of cancer. If the question is should a specific label indication, a label claim, be that, I would vote no. If in the description of the clinical trials, as you mentioned, Dr. Wolfe, there should be a description of what occurred, that's how I interpreted my vote. I would vote yes. But if the labeled indication, the labeled claim -- I would vote no, and I must say I'm sorry. I misunderstood what the vote was then.

DR. WOLFE: Looking at the different package labels, I could see this reading that a risk reduction was demonstrated using Photofrin. A durability beyond 2 years has not been demonstrated, something to that effect. Does that sound like something you'd be comfortable with?

DR. HOUN: Well, that's what we're asking advice on. The indication sought is for the ablation of high-grade dysplasia in Barrett's esophagus among patients who refuse esophagectomy -- and I know you wanted to talk more about that -- and who are in overall good health. That is not a claim, an indication for cancer risk reduction. This question is saying does the data support that as part of an indication. We hear that we definitely

should be including the 2-year follow-up data in the clinical trials section. I want to know and the sponsor has asked for you to consider the broader indication for this. So we wanted to just get your input.

DR. WOLFE: Dr. Camilleri, then Dr. Goldstein.

DR. CAMILLERI: I'm wondering whether other people like Dr. Mangel will want to reinterpret this question in light of his comment. I felt that none of these questions really address the practical way to manage this problem, and if you look at the non-C1 responders -- because nowhere in these questions are we going to address it -- there are a lot of people. There are enough people, up to 25 percent I think I was told by Dr. Carpenter, that actually go on to develop cancer even in the PDT group. And that's what's concerning me, and I wanted to explain why my vote was a no.

I do believe that there is a numerical reduction. We all saw that numerical reduction. But my concern is that if we do not qualify and give advice to the agency as to what sort of follow-up is going to be necessary and how the follow-up has to be not just surveillance but what would be the milestones that would lead to different types of therapy, then I think I'd be concerned that this move forward with a blanket approval.

DR. WOLFE: Dr. Goldstein?

DR. GOLDSTEIN: I feel absolutely certain that the agency has gotten the gist of the committee's views, and I think I would also suggest to you all that there are facts of the study, the 2 years, the reduction of risk, et cetera, all as we say, res ipso loquitur. The facts speak for themselves. The distinction or the transition from that to a claim and what can or cannot be in the claim is something to be left, I think, between the agency and the sponsor.

DR. WOLFE: Again, I'm looking at this just very literally, and I don't think that anybody here is claiming that this is a panacea, that it's complete, total risk reduction. It is a risk reduction is what you're asking.

DR. HOUN: And also help us with in whom it's indicated. Is it as an alternative to esophagectomy? Is it an alternative to surveillance? How do you want to position this given what you've seen in the data and what do the data support?

DR. WOLFE: Well, that's actually a separate question in a way. So we'll have to add that question on. In whom should this be indicated? The sponsor has asked for in patients who refuse esophagectomy who are in overall good health, which is in many ways, we point out, an oxymoron because most of the patients who refuse surgery

are not in good health.

Ms. Cohen.

MS. COHEN: I'm just reading what it says here. It says in the Photofrin PDT group, 18 patients have progressed to cancer and another 18 had other therapeutic intervention because of persistence or recurrence of HGD. So you can't say positively that it cures it in 2 years. I think that's very dangerous.

DR. WOLFE: Ms. Cohen, no one is saying it cures it --

MS. COHEN: Well, I'm saying it.

DR. WOLFE: But I'm going to ask the oncologists here because the oncologists treat cancer.

MS. COHEN: I can tell you I don't want someone to tell me that it cures something if you don't know it.

DR. WOLFE: How many drugs offer a 100 percent cure rate?

MS. COHEN: Well, that has nothing to do with the issue.

DR. WOLFE: Versus a risk reduction.

DR. KELSEN: Not many.

DR. WOLFE: Do any?

DR. KELSEN: None. I think this is risk reduction. It just means fewer people get the disease.

DR. WOLFE: Obviously, you would tell the

person, when we talk about other forms of therapy, this one is available to you. Here are the data. We have numerous situations in which we have different forms of therapy.

Let me raise a simple one and that's reflux disease. People require long-term medical therapy. What's offered to them is they could have long-term medical therapy. They can be treated with laparoscopic fundoplication or they could even undergo endoscopic therapy which is now approved. So there are different forms. This is much more serious, but nevertheless there are choices and we explain the different choices to patients and understand that none of these are perfect. Esophagectomy is also not perfect.

Dr. Carpenter.

DR. CARPENTER: At some point we should talk about the "in good health," and at some point I think we should make advice about how to use this. It should include a statement which is from the data which is of those people who did not respond, there was a very high risk of malignancy and 50 percent over the 2-year period and that alternative therapies should be strongly considered.

DR. WOLFE: Again, shall we first just answer this specific question? Has a risk reduction been demonstrated in cancer over the 2-year period? Do you want

us to answer that question first?

DR. JUSTICE: Yes.

DR. WOLFE: Okay. So let's just go by roll call. Has a risk reduction been demonstrated over the 2-year period of observation? Which way did we go last time? Dr. Camilleri. Oh, no. We started with you last time. Dr. Mangel, we'll start with you.

DR. MANGEL: If it's for a statement in the label in clinical trials, I vote yes. If it's for a formal indication, I vote no. I vote no if it's for a formal indication. I vote yes as a statement in the clinical trials. The intent of the statement changes my vote. I'm sorry.

DR. WOLFE: Do you want us to clarify any further? I think the question is, has a risk reduction been demonstrated?

DR. HOUN: I think if you would help us in terms of an indication. Right now I read to you the indication was treatment is indicated for the ablation of high-grade dysplasia. That is a different indication than indicated to reduce the risk of esophageal cancer. So vote on the indication. That helps us the most, and that's probably the most important for --

DR. WOLFE: I want to clarify among my colleagues here. We all agree that high-grade dysplasia

can advance to esophageal adenocarcinoma. Correct? And if it's ablated, doesn't if A equals B, B equals C?

DR. HOUN: If the data support that, tell us you say that that's part of the indication. Okay? If you do not believe the data support that, you can say no, that the cancer risk reduction should not be part of the indication.

DR. WOLFE: Dr. Camilleri.

DR. CAMILLERI: Mr. Chair, I don't understand why you want to add something to the indication that the sponsor is suggesting.

DR. WOLFE: I'm not saying I want to do anything. I haven't voted yet. But I'm looking at this from a scientific perspective and what does the data actually demonstrate and why are we ablating high-grade dysplasia in the first place. Why are we doing it? What is the purpose of it?

DR. MANGEL: To me, Dr. Wolfe, the difference is the practical extrapolation from if it's a sentence talking about what happened in the clinical trials section of the label, if it's information, it helps in guidance for the physician versus if it's the indication. To me, like many other drugs, the propensity is too great if it's in the indication, if it's a formal indication for the drug, that if it's good for 2 years, it's good for 5 years, it's

good for 10 years, it's good for life when it's a formal indication versus if it's clearly described in the clinical trials what they saw and what they didn't see. So to me that's why my vote, with the same data, varies depending on where in the label the sentence or statements are.

DR. BRAWLEY: Can I quickly ask, Dr. Mangel? Are you saying that cancer risk reduction is not a reason to get the treatment, but --

DR. MANGEL: No. I think cancer risk reduction is the reason to get the treatment. For me the data are not robust enough in terms of longevity to have it as the formal indication, where I would agree the extrapolation, as Dr. Wolfe was saying, of ablation of high-grade dysplasia is a reduction in cancer, but I would not allow it to be discretely said.

DR. WOLFE: We have a difference of opinion. The question reads 2-year. I think the data you've shown showed a 2-year reduction in the risk of cancer. Didn't the data show that? Okay. So again, keeping that in mind, we can then discuss and then vote.

Ms. Cohen, you have a question or comment?

MS. COHEN: Yes, I do. "Adequate" says something. It's qualifying and if it were adequate in the 2 years, then you wouldn't need a 5-year. So you're already saying that it's adequate and therefore you can do

it and it's going to be fine, but that's not the case because you want to continue to study it.

DR. BRAWLEY: Perhaps I can speak up here as a card carrying epidemiologist. When we talk about risk reduction, we very frequently talk about risk reduction over a defined period of time. Sometimes we talk about risk reduction over that defined period of time being one's life. Sometimes we talk about risk reduction over a 2- or a 5- or a 10-year period of time.

MS. COHEN: You know what bothers me, Dr. Brawley, is that, again, we're looking for people who are experts in their field who will be able to explain this, and it all depends upon the health delivery system that you get the full information.

DR. WOLFE: Dr. Camilleri, you had a question or a comment?

DR. CAMILLERI: I was going to ask whether anybody knew enough about the natural history of risk reduction in high-grade dysplasia over a 2-year period to determine whether that period of time is sufficient to be sure that there wouldn't be a cancer developing subsequently.

DR. WOLFE: I think the question was rephrased, however, and we're now looking at the adequacy of the 2-year period. Is that good enough? I don't think any of us

think that's good enough. We rephrased the question. The question was, as Dr. Houn just mentioned, would the label include a statement saying that there's a risk reduction -- again, I may be paraphrasing you incorrectly. Do the data demonstrate a risk reduction in cancer in patients with high-grade dysplasia treated with this modality? Is that correct? Do you want that information? Do you care?

DR. HOUN: If this is too difficult for the committee, I'm happy to table this. But again, I think it's the distinction between describing it in the clinical trials versus allowing the drug to be advertised for cancer risk reduction. We wouldn't use the word "prevention," but it could be --

DR. WOLFE: Reducing the risk.

DR. HOUN: -- reducing the risk. And if you feel that 2-year data are supportive enough for that indication or maybe they could get the risk reduction indication after 5 years. That is the issue.

DR. BRAWLEY: Can I make the following statement? I think most of the committee would agree with this, I hope at least. I believe that the scientific data suggests that this intervention reduces an individual's risk of getting the diagnosis of esophageal cancer over the 2-year period of time. I do not believe that the data is robust enough to say anything beyond 2 years, and I do

believe that people should undergo observation beyond the 2-year period of time for both dysplasia, as well as esophageal cancer.

DR. WOLFE: Once again, we're saying exactly the same thing.

DR. LEVINE: Why don't we vote on that --

DR. WOLFE: We're going to vote on that exactly.

DR. LEVINE: -- on Dr. Brawley's statement, and then it's clear?

DR. WOLFE: The question then is sort of restated. Do the data demonstrate a risk reduction over the 2-year period in the development of adenocarcinoma of the esophagus in those patients treated with this modality?

DR. HOUN: It's not do the data show that. It's is the data adequate to give them an indication.

DR. BRAWLEY: For 2 years.

DR. HOUN: For 2 years. If you're now rewriting it so it's 2 years.

DR. LEVINE: A point of information.

DR. WOLFE: Yes.

DR. LEVINE: Dr. Houn just said she didn't want it construed by virtue of advertising that it could be advertised as a cancer preventive. If it was in the label that it was from the scientific study to 2 years, that's

all right, but what we're clearly saying is we don't think that it's preventive over a longer period of time. So you're putting yourself in a box if we vote on is it 2 years preventive.

DR. BRAWLEY: No. Risk reduction.

DR. WOLFE: They're very different.

DR. LEVINE: Even risk reduction I think can be construed, if there's no follow-up to point out that we do not think it's adequate for longer term.

DR. HOUN: If you want to caution the agency that the data not be misconstrued that way and you're concerned that if it's put in the indication, it would be misconstrued, you could state that.

When the drug is approved and the indication -- that is what is the black and white -- you know, the PPI. Acid reducer, heartburn treatment, GERD treatment. The goal is for the -- what is the indication they can promote. Now, they can put in smaller print what's found in the clinical trials. So it's a very important aspect on how you want the drug to be used and what you think the data support for the indication.

DR. WOLFE: So, again, I'll ask, are we voting on do the data support a 2-year risk reduction in the development of adenocarcinoma of the esophagus? That's the question we're asking right now.

DR. HOUN: Do the data support an indication for 2-year esophageal cancer risk reduction?

DR. WOLFE: Dr. Goldstein.

DR. GOLDSTEIN: Let me see if I can help. This may turn out to be a semantic issue at the end.

If you use the words "drug X is indicated for the reduction of the risk of cancer for 2 years," that's one thing. If you agree that the data support that simple fact, but the wording would go into the clinical trials section, it would go into the labeling -- it's established. It's in the body of the text, but not necessarily an indication for its use. Penicillin is indicated for the treatment of streptococcus. Penicillin is indicated for the treatment of and so forth and so on. Here what they're trying to do is, is it an indication? Is the evidence sufficiently robust to, if you will, elevate it to a status of an indication for its use? Or is the data there? They've confirmed that, which I believe they have, that it does do what is said here for 2 years, but not necessarily as a trigger for somebody to use it for that purpose. That's the distinction.

DR. WOLFE: Any other clarification needed before we vote? Ms. Cohen.

MS. COHEN: If you can add a caveat in the 2-year clinical trial, 18 patients had progressed to cancer.

I think you have to have full disclosure. Not to do this is a failure to state a material fact in the language of the FTC. If I'm one of the 18 people who progressed to cancer, I'd be very upset if it wasn't disclosed.

DR. JUSTICE: That would go in the clinical study section.

DR. WOLFE: So once again, we're voting on whether the data supports a risk reduction, a reduced risk, in the development of cancer over the 2-year period of time. That's what we're voting on. We're going to do it by roll call. Dr. Mangel.

DR. MANGEL: As part of the indication, I say no.

DR. WOLFE: The answer is no.

DR. MANGEL: I say no.

DR. WOLFE: Dr. Kelsen.

DR. KELSEN: Yes.

DR. WOLFE: Ms. Cohen?

MS. COHEN: No, not unless there's a full disclosure.

DR. GILLETT: Yes.

DR. WOLFE: I'll just put a little caveat ahead of time, just one brief statement, again we already said that it reduces high-grade dysplasia, which causes cancer. Therefore, I say yes, it's been demonstrated to reduce the

risk of developing cancer.

DR. WOLFE: Dr. Levine?

DR. LEVINE: No, because I think it will be construed conceivably for advertising purposes.

DR. WOLFE: Dr. Brawley.

DR. BRAWLEY: Yes.

DR. WOLFE: Dr. Shih.

DR. SHIH: Yes.

DR. WOLFE: Dr. Carpenter.

DR. CARPENTER: No.

DR. WOLFE: Dr. Camilleri.

DR. CAMILLERI: No.

DR. WOLFE: Well, we helped you out a lot. It's 5 to 5.

(Laughter.)

DR. HOUN: Thank you.

DR. WOLFE: Now, the one thing I do want to ask, not to change somebody's vote, but you asked about as long as there's a full disclosure. They said there would be a full disclosure.

MS. COHEN: I don't know what the advertising is going to do.

DR. WOLFE: I don't think there's going to be a big campaign on this.

MS. COHEN: Oh, please.

DR. WOLFE: This is an orphan drug more or less. It's not an orphan? This is an orphan. So, again, I don't see big, gigantic ads being placed.

But that's beside the point. We voted. It's 5 to 5.

Dr. Carpenter.

DR. CARPENTER: Could we have some statement or vote on the part about "in good health"?

DR. WOLFE: We'll get to that in a second. I first want to finish what we have here, and that is we pretty much all agreed -- or most of us agreed -- that patients need to be followed up. So how frequently should patients who have undergone Photofrin PDT be monitored by esophagoscopy? This is following the procedure itself. They have it. There's no visual evidence of Barrett's high-grade dysplasia by biopsy. How often should patients be endoscoped?

Do you mind, no offense to anybody else, if we start with the gastroenterologists first since we have experience in this area? Dr. Camilleri.

DR. CAMILLERI: I was impressed with Dr. Overholt's statement and that is in the first year, every 3 months, and after that, if the patient is clear, every 6 months, and then beyond that, probably every year.

DR. WOLFE: Dr. Levine.

DR. LEVINE: I concur, yes.

DR. WOLFE: I agree. That sounds exactly like what I would do too.

Now, do you want to fight with us, any non-gastroenterologists here?

(Laughter.)

DR. WOLFE: Dr. Justice.

DR. JUSTICE: Could you just clarify this? Every 6 months for how long?

DR. WOLFE: Q 3 times 1 year; q 6 the second year; then q 1 after that.

That was much faster than I thought that was ever going to be.

(Laughter.)

DR. CAMILLERI: Please help me. Are we ever going to vote on the proposed indication?

DR. WOLFE: That's what we're doing right now. Now, the indication talked about which patient population. Are you talking which patient population?

DR. CAMILLERI: And the specific request from the sponsor with the specific wording.

DR. WOLFE: Yes. That's the patient population, high-grade dysplasia in those people who are healthy. Okay. So let's discuss that now because I think several of us have issues with that specific definition.

We started with you, so we'll start with Dr. Goldstein this time.

DR. GOLDSTEIN: I'm sorry, Mr. Chairman.

DR. WOLFE: Let's specifically look back to your first page, and it says here in italics underneath "new drug application (NDA) 21-525," "PDT with Photofrin is indicated for the ablation of high-grade dysplasia in Barrett's esophagus among patients who refuse esophagectomy and who are in overall good health."

So do we feel that is the appropriate target population? Is that what the indication should say?

DR. GOLDSTEIN: My feeling is that the language needs to be cleaned up, that in fact it is confusing, to me at least, as written, and in some elements contradictory, as I think Dr. Carpenter has pointed out earlier.

DR. WOLFE: Can I offer an alternative? Then we can discuss from there. How about is indicated for patients with high-grade dysplasia -- among patients with high-grade dysplasia? Period. It's an alternative form of therapy. Does anybody else want to add to that?

DR. GILLETT: I think it's really important to do that because you have both those who are refused esophagectomy and those who refuse esophagectomy. You have all stages of health. There so far is no indication of adverse interaction with other illnesses or states of

health. I think it confuses the issue to have the extra verbiage in there.

DR. WOLFE: Dr. Kelsen.

DR. KELSEN: My only concern about that is by not having it in the indication a statement about esophagectomy one way or another -- and I'll also have a statement -- is I'm just a little bit worried that people will not even consider what is still right now the standard of care. And I wonder if the agency would be comfortable with something that says among patients who are either not candidates for or who refuse esophagectomy and can tolerate the proposed treatment plan, which would allow you to still clue a physician in -- it's hard to believe somebody wouldn't know this, but it would clue a physician to the fact that the alternative option is surgical intervention.

DR. WOLFE: I agree. I think the information in the PI should say something to the effect that a direct comparison in a study comparing this phototherapy to esophagectomy has not been performed, and esophagectomy still is considered the gold standard of therapy so that that is indicated in there and physicians understand and patients are made to understand that they are being treated with something which has not been tested against the gold standard. But that's their right in my view to choose which form of therapy they want taking into account, again,

organ preservation, potential quality of life. They need all the information available to them. This doesn't differ from a lot of things we do. A lot of things are offered to patients.

DR. GOLDSTEIN: Mr. Chairman, I wonder if I might be allowed to suggest perhaps alternative language, and the indication would read photodynamic therapy with Photofrin is indicated under special circumstances as alternative therapy for the ablation of high-grade dysplasia in Barrett's esophagus. Period.

DR. WOLFE: I'm not sure. Do you want to define the "under special circumstances"?

DR. GOLDSTEIN: Well, the point is the special circumstances clause is meant to refer those interested to those special circumstances such as central reference or regional reference experts or laboratories or to allow the agency I think to interpret with the sponsor those special circumstances. They can give fuller meaning to the term "special circumstances."

DR. WOLFE: Ms. Cohen.

MS. COHEN: I used to draft my own cease and desist agreements, so you have to forgive me. I would say that photodynamic therapy with Photofrin could be or might be considered in the ablation so that you're saying there are other things that might be done, but it isn't saying

definitely it must be. It's to be considered. And then it begs the question then what other things would you offer me.

DR. WOLFE: I'm going to come back again to an example which is not nearly as dire. Come back to the case of GERD. H-2 blockers are indicated in the treatment of erosive esophagitis. Proton pump inhibitors are indicated in the treatment of erosive esophagitis. It doesn't qualify which therapy is better. What I'm proposing here is very broad. It's not that broad because I don't know how many patients we're talking about. But it's a broad definition which is a decision made by the physician and patient together. So I'm proposing it as a form of therapy for the treatment of a disease.

DR. BRAWLEY: Mr. Chairman, can I second your motion?

DR. WOLFE: What we can do is we can put that up, and if it's voted down, we can then pick another definition. How does that sound instead?

Dr. Levine.

DR. LEVINE: I think the gastroenterologists here are a little skewed and more sophisticated, if I can say, with this disease than the public or other physicians who will be referring to them. I think although it's obvious, as Dr. Camilleri pointed out to us, that it's

sufficient to stop and just say high-grade dysplasia as an indication, I agree with the previous comment. I think we probably have to put something about esophagectomy because that is the gold standard, and I think if it's not there in the indication, it may get lost to our colleagues who are not nearly as sophisticated in gastroenterology.

DR. WOLFE: Dr. Carpenter.

DR. CARPENTER: Could you just say who do not undergo esophagectomy?

DR. WOLFE: Who choose not to undergo esophagectomy.

DR. CARPENTER: Who do not, and leave it open.

DR. KAMINSKAS: I just thought of combining both the old phrasing and new phrasing by the sponsor because the old phrasing, among patients who are not considered to be, sort of implies a physician's decision.

DR. WOLFE: No, it doesn't. It implies a decision was made between the physician and --

DR. KAMINSKAS: Among patients who are not considered to be candidates for esophagectomy.

DR. WOLFE: But that could be the patient considering that as well.

DR. KAMINSKAS: But I was thinking of among patients who refuse esophagectomy or who are not considered to be candidates for esophagectomy.

DR. WOLFE: Let's vote on this. I like the language that was added. The therapy is indicated for the ablation of high-grade dysplasia in Barrett's esophagus among patients who do not undergo esophagectomy.

DR. GOLDSTEIN: Would you accept, addressing Dr. Levine's earlier comment and my earlier suggestion, as an alternative to esophagectomy? Because that in fact is what it is, an alternative to esophagectomy.

DR. WOLFE: Dr. Camilleri.

DR. CAMILLERI: I'm sorry. That almost implies that this is as good as, and I'm worried about that terminology.

DR. GOLDSTEIN: Well, I certainly didn't mean to imply that.

DR. WOLFE: By saying who don't undergo esophagectomy implies to me -- it's implicit -- that esophagectomy is the preferred form of therapy.

Dr. Mangel.

DR. MANGEL: I favor, if we're about to vote, going back to Dr. Kelsen's proposal. When we look at what was actually done in the study, the population was those who refused esophagectomy, and then his proposal extended it for those who are not candidates for esophagectomy. The data were collected in individuals who refused esophagectomy. Results in a different population may be

different. Probably not, but could be different.

DR. WOLFE: Could I ask the sponsor a question? Why were these patients considered in good health and refused esophagectomy? Were questions asked why they refused it?

I'd really prefer to be as broad as the statement we just said, and let's vote on it. If we vote it down, then we'll change the language. So again, we're going to vote on this right now, unless someone really feels strongly we should discuss this further. It's going to be saying the following. Photodynamic therapy with Photofrin is indicated for the ablation of high-grade dysplasia in Barrett's esophagus among patients who do not undergo esophagectomy.

Dr. Mangel.

DR. MANGEL: Yes, I vote in favor of it.

DR. WOLFE: Dr. Kelsen.

DR. KELSEN: Yes.

DR. WOLFE: Ms. Cohen.

MS. COHEN: No.

DR. WOLFE: Dr. Gillett.

DR. GILLETT: Yes.

DR. WOLFE: Yes.

Dr. Levine.

DR. LEVINE: Yes.

DR. WOLFE: Dr. Brawley.
DR. BRAWLEY: Yes.
DR. WOLFE: Dr. Shih.
DR. SHIH: Yes.
DR. WOLFE: Dr. Carpenter.
DR. CARPENTER: Yes.
DR. WOLFE: Dr. Camilleri.
DR. CAMILLERI: Yes.
DR. WOLFE: 9 to 1.
Does that help you a little bit?
(Laughter.)
DR. HOUN: Yes.
(Laughter.)
DR. WOLFE: It's now 10 to 1.
(Laughter.)
DR. WOLFE: All right. Now let's move on to the next question. Is the safety profile of Photofrin PDT acceptable? Keeping in mind that there was some toxicity in a very serious disorder, was this acceptable? We'll start with Dr. Camilleri.
DR. CAMILLERI: Yes.
DR. WOLFE: Dr. Carpenter.
DR. CARPENTER: Yes.
DR. WOLFE: Dr. Shih.
DR. SHIH: Yes.

DR. WOLFE: Dr. Brawley.
DR. BRAWLEY: Yes.
DR. WOLFE: Dr. Levine.
DR. LEVINE: Yes.
DR. WOLFE: Yes.
Dr. Gillett.
DR. GILLETT: Yes.
DR. WOLFE: Ms. Cohen.
MS. COHEN: Believe it or not, yes.
DR. WOLFE: Wait. I have to sit down for a second.
(Laughter.)
DR. WOLFE: Dr. Kelsen.
DR. KELSEN: Yes.
DR. WOLFE: And Dr. Mangel.
DR. MANGEL: Yes.
DR. WOLFE: We have a unanimous vote. We could take like a 30-second drink break if you'd like.
(Laughter.)
DR. WOLFE: Moving to the last question. The applicant is continuing to collect patient follow-up data in PHO BAR 02 study for an additional 3 years. PHO BAR 01 and PHO BAR 02 taken together will provide a maximum of 5 years of follow-up for patients in the two arms of the study. Is this 5-year period adequate to demonstrate

cancer risk reduction in high-grade dysplasia patients?

We'll start -- who did we start with last time? Should we start in the middle this time? We'll start in the middle. We'll start with actually Dr. Levine.

DR. LEVINE: In the ideal world, I'm all a 5-year follow-up, real 5-year follow-up at the end of treatment. And I would like to see it in the original study and not in additional arms of the study that were previously used back in '91 or '94 when it was the first date it started. I can't remember the dates.

DR. MARTIN: 1993.

DR. LEVINE: 1993. I think, if I'm correct, most of those studies were done exclusively in one unit, is that correct, in Tennessee?

SPEAKER: (Off microphone.)

DR. LEVINE: So they were done by one investigator in one unit.

DR. WOLFE: You're continuing this study for an additional 3 years. Correct?

DR. MARTIN: Yes. This is the PHO BAR 01 study that we are continuing for 3 more years. So we have given you the results at 2 years. We are extending the observation period for 3 more years. The study is called PHO BAR 02. And those are the original patients that were in.

DR. LEVINE: By one investigator.

DR. WOLFE: No, no. It's a multicenter. It's the same patients.

DR. LEVINE: I stand corrected.

I don't see a problem with that. I think it's mandatory to have a good output, and I don't know what the number of years should be, but I think 5 is a very good guess estimate.

DR. WOLFE: Dr. Brawley.

DR. BRAWLEY: I hate to do this. Remember, it's a maximum of 5 years. It's not everybody at 5 years or beyond. Again, I think the data that might have a median follow-up of 4 years would indicate a decrease in risk for that 4 years and probably indicate a decrease in risk for the remainder of the life of the patient. But on technicality, the answer to the question in my mind is no.

DR. WOLFE: Dr. Shih.

DR. SHIH: Yes, I have a problem with that maximum 5 years. I thought it was a minimum of 5 years. So maybe there's some consideration of the maximum of 5 years problem.

DR. WOLFE: Before we go any further, can I ask a clarification of the sponsor? Because I really want to know. What do you intend to do here? Why don't you let us know? Do you intend to get the patient to 5 years and stop

the study? How many patients do you intend to take to the 5-year period of time?

DR. MARTIN: When patients will have been surveyed for 5 years in the trial, the trial will be terminated in these patients.

DR. WOLFE: After all the patients have been --

DR. MARTIN: As many patients that we can follow through until 5 years.

DR. WOLFE: Obviously, if they drop out or die, then --

DR. MARTIN: Yes.

DR. WOLFE: But those patients who are still alive and willing to participate.

DR. MARTIN: Yes.

DR. WOLFE: So it's all the patients that are available. There will be dropouts, I assume, for several different reasons, but otherwise, you're extending the study to 5 years now.

DR. MARTIN: Yes, except the patients who will discontinue therapy for any event. But the trial is going on.

DR. KELSEN: You mean a minimum of 5 years, not a maximum of 5 years.

DR. DONNER: The intention is to follow all the patients for 5 years. Some inevitably will not be followed

for 5 years for the reasons that --

DR. WOLFE: But some actually go longer than 5 years possibly.

DR. DONNER: Yes, absolutely.

DR. WOLFE: So your intent here is to continue the study -- make it a 5-year instead of a 2-year.

DR. DONNER: Yes.

DR. WOLFE: Does that provide some clarification?

DR. BRAWLEY: I think it's misworded here. I agree with Dr. Kelsen. It's a minimum of 5.

DR. WOLFE: I agree. Well, you know what the question should say. It's basically saying by changing it to a 5-year observation period after therapy, is that adequate to say now that --

DR. BRAWLEY: Yes. I would change my vote to yes in that instance.

DR. WOLFE: Dr. Shih.

DR. SHIH: I really think that the minimum follow-up is ambiguous here. I asked the question previously, you know, if a patient discontinued the therapy, are they followed up by their endoscopy? And I heard they returned to their private physician and they never collected data. That does not imply follow-up. Follow-up means that you monitor. You collect the data.

So I would like to really have them clarify that. If they didn't collect the data, they didn't follow up.

DR. WOLFE: Can the sponsor clarify? Will the patients beyond year 2 be having yearly endoscopies?

DR. SHIH: Even after they switched therapy, even after they discontinue. The omeprazole group, even they started a new intervention. When you say you follow up for at least 24 months, that means you still collect their data. According to your protocol design, under surveillance, you still go to endoscopy.

DR. MARTIN: Dr. Colin, do you want to comment on it?

DR. COLIN: Yes, thank you, Francois. Just an additional clarification about the long-term extension of the PHO BAR 01 study which is called PHO BAR 02. We have decided to go on with the follow-up of these patients in order to gather long-term efficacy and safety data, but up to 5 years. None of the patients will be followed in the PHO BAR 02 study beyond 5 years. They may be followed locally by their treating physician. We're not prospectively collecting the efficacy data on these patients because they will not be in the PHO BAR 02 study anymore.

Moreover, I have also to mention that 61 patients only are being followed in this long-term

expansion because many clinical investigators did not accept to participate in the PHO BAR 02 long-term extension because they were already convinced of the therapeutic benefits of PDT Photofrin for their patients.

DR. WOLFE: The FDA will have to help us here with the number of patients you're going to require for a long-term study. So you're saying there are 60 patients in which group?

DR. COLIN: 61 total; 48 patients in the active PDT Photofrin treatment arm, and only 13 patients in the omeprazole control arm.

DR. HOUN: So when you say you will follow up the 61 patients, is it that there will be no lost to follow-up because you will continually get information on them?

DR. MARTIN: Yes.

DR. HOUN: So if they took another intervention, if the omeprazole group, the 13, and they go to esophagectomy or PDT, you still will follow up on them?

DR. MARTIN: No, not if they have received another intervention for a reason. If it is for cancer, it would be counted as a treatment failure. If it is for return of high-grade dysplasia, it is a treatment failure. After the patient has the esophagus removed, they won't be followed because they will then be outside the protocol.

DR. COLIN: Except, Francois, for cancer and patient survival, we will still collect data for those patients even if they reach an endpoint in the PHO BAR 02 study. Cancer and survival only.

DR. MARTIN: We will account them, but we will not collect data. We cannot do biopsies on an absent esophagus.

DR. WOLFE: I want to clarify just one thing before Dr. Carpenter speaks. Remember, the omeprazole group is, in essence, a surveillance of high-grade dysplasia which has been only advocated to my knowledge by one group, and that's the people in Chicago. Most don't feel people patients with high-grade dysplasia should be surveyed, except that group does. Most people have felt they should have some type of intervention. So in a way, this is very important data on patients who are just being treated with a PPI, nothing else.

Dr. Carpenter.

DR. CARPENTER: Some of this is semantic. I understand that people who have had another therapy won't be followed up and then they won't be getting repeat endoscopies by same group. I think what we want to know is are you going to collect survival data and are you going to collect data on whether or not they get cancer on all the participants.

DR. WOLFE: Are you going to collect that data?

DR. COLIN: Yes. Yes, we will by telephone contact with the patients.

DR. WOLFE: I don't think that the FDA is going to say, okay, 3 years ago we decided it was okay, no problem, without looking at the data 3 years from now. Is that correct? You're going to look at it again to see what kind of claims. Someone else besides me will be sitting here telling you all that information. So we're just looking, theoretically now, in principle, if this is a successful study and data are provided 3 years down the road and it does show that this is a durable form of therapy, will then be able to say, yes, it is indeed durable for a period of 5 years. Is that what you're saying?

DR. HOUN: Yes.

DR. WOLFE: Okay. Now, keeping that in mind, Ms. Cohen, sure.

MS. COHEN: I'm sorry. What about post-marketing data? Are you going to forget that?

DR. WOLFE: I'll speak for the company. You're going to do post-marketing surveillance, aren't you?

MS. COHEN: Well, I think you ought to think about it and say that it will or will not be done.

DR. WOLFE: It's required, isn't it?

DR. HOUN: Yes.

MS. COHEN: The way this is worded, it isn't included in it and that worries me.

DR. WOLFE: That's omission. It's required by law that they do post-marketing surveillance. So they will do it.

So keeping that in mind, can we start again with Dr. Levine?

DR. HOUN: I just want to make sure Dr. Shih's issues -- did you have any other questions about this follow-up?

DR. SHIH: Yes. I think they clarified it that they provide up to 5 years follow-up. They have clarified that. So my answer is this is not adequate.

DR. WOLFE: Let's just start again. Dr. Levine, are you still happy?

DR. LEVINE: With minimum or with maximum, I think the gist of it, as long as the 5 years is in there, I think it's sufficient. I'd say yes.

DR. WOLFE: Dr. Brawley.

DR. BRAWLEY: It's barely adequate.

DR. WOLFE: So a small Y.

(Laughter.)

DR. WOLFE: Dr. Shih. You said no. Correct?

DR. SHIH: Yes. I confirmed I said no.

(Laughter.)

DR. WOLFE: Dr. Carpenter.

DR. CARPENTER: Yes.

DR. WOLFE: Dr. Camilleri.

DR. CAMILLERI: A barely Y.

(Laughter.)

DR. WOLFE: Dr. Mangel.

DR. MANGEL: Yes, and I would add the comment after the 5-year data, I would be comfortable having it in the indication.

DR. WOLFE: Dr. Kelsen.

DR. KELSEN: Yes.

DR. WOLFE: Ms. Cohen.

MS. COHEN: If maximum is taken out and just provide 5 years.

DR. WOLFE: Dr. Gillett.

DR. GILLETT: Yes, minimum.

DR. WOLFE: And mine is a yes also.

Is there anything else you would like us to do besides turn the microphone on when you're speaking? Dr. Camilleri.

DR. CAMILLERI: I'm still a little concerned about what information and guidance will be given to the practitioners with regard to that follow-up period in the first 6 months because I found the data a little bit

difficult to follow because the denominator seems to be shifting all the time. But it seems to me that there are 19 to 23 percent, depending on which data you see from the agency or from the sponsor, that don't respond. Now, clearly we know what to do with those patients.

However, if you look at the Kaplan-Meier curves, whether it's for the C1, C2, C3 endpoint, there's about a 30 to 50 percent of patients in the first 6 months that fail to maintain that response. And the question here is, should there be recurrent treatment for failure to maintain the response? That's one question.

How are practitioners going to be able to use this therapy? And should there be any advice in the information provided to practitioners? What educational programs are going to be offered? I'd like to hear a little bit more about that, please.

DR. WOLFE: Will someone from the sponsor please address this issue? I'll choose someone if you don't --

DR. MARTIN: I don't know what to say to the questions of Dr. Camilleri.

This study that we've presented, the pivotal study, is a study started 5 years ago. We're planning to continue observing patients for 3 more years. This is the largest single randomized study evaluating a therapeutic

modality to treat and correct or ablate a premalignant condition. Up to this time, there are some guidelines to survey patients with high-grade dysplasia. No matter what we can say today, high-grade dysplasia will remain a pre-neoplastic disease. Patients should either receive esophagectomy, which is another treatment modality, but to my knowledge, has never been tested as much as we are testing our proposed treatment modality at present. And no other treatment modalities that are used by individual physicians have suffered or sustained any prospective randomized evaluation for such a long period.

So I think standard of care will continue to exist for whoever chooses it, but an alternative therapy is there that at least with data statistically significant shows that this condition be ablated at least for 2 years and perhaps longer. So this is all I can say. I don't think we can individualize all treatments or all decisions in whatever label or product monograph.

DR. WOLFE: Can I just ask a question of the FDA? Will there be in the label recommendations that endoscopy should be performed? So you'll have all that in there. Is that one of the questions you're asking?

DR. CAMILLERI: I want to hear Dr. Overholt because I don't think I got an answer. Sorry.

DR. OVERHOLT: I am involved with the company

in developing a training program. We have had one. We've got one scheduled in another month and one two months after that. It's a direct observation of patient care delivery of the PDT to the patient, followed by a day of lecture and a half a day of, in the lab, hands on actual mentoring and training. Out of that program, we feel that it's adequate for credentialing purposes in hospitals.

DR. WOLFE: Michael, are you happy with that?

DR. CAMILLERI: So if somebody has a C3 lesion back, if they have Barrett's back, at 6 months in follow-up, does the practitioner then know what to do?

DR. OVERHOLT: Call me.

(Laughter.)

DR. OVERHOLT: If they have a continuation of Barrett's mucosa after PDT, we would encourage, based on long-term data, that the patient be followed with whatever modality is used for ablation of the residual Barrett's. They do know that. They will know that.

DR. CAMILLERI: I'm happy that there appears to be educational materials that will be developed.

DR. WOLFE: Yes. I don't think it's completely decided, but it looks like it's being addressed very seriously.

Any other questions or comments? Any questions from the FDA?

DR. HOUN: Is the company's plan that this type of training and lecture and lab be part of the approval package? In order for a GI guy to do this, they undergo company training and lab and lecture?

DR. MARTIN: I think I can commit today that we could have a fair discussion with the agency considering your question here.

DR. HOUN: Would it be the recommendation of the committee that such training of lab and lecture be part of this package or voluntary?

DR. WOLFE: I would prefer just right now that we say training would be required, mandatory for using this, or something to that extent. You can't just go ahead and give this. It's not like taking a pill.

DR. CARPENTER: Highly recommended.

DR. LEVINE: I had a previous concern that even though this is an orphan drug and it might be used in a small number of people, if it's as simple as the sponsor states and the learning curve is so quick and it's basically a quicky course, whether it's going down overnight, 2 days, 3 days, and the reimbursement is large for Photofrin therapy -- I can guarantee it is large for repeated dilatations in the 36 percent that have strictures -- you will be getting a flood of people who are rushing out to use this new toy, and I think it should be mandatory

that they're either regional centers and that there should be an insistence that there's an expert level obtained. Whether it can be done in a quick course, if it's that simple, fine. I think that will discourage overuse and probably keep the numerator rather than the denominator eventually of the high-grade dysplasia being at a proper level rather than the 250 percent almost level of patients biopsying and misinterpreting the endoscopic appearance. So between the requirement that we recommended about expertise in pathology, I think there should also be comparable expertise in doing this.

DR. WOLFE: I was involved with the Stretta procedure from the get-go. This is analogous although this is actually a steeper learning curve because it sounds like one will be enough. I had people who were interested in doing it come and do some endoscopy with me. They just spent an afternoon with me and people in the area, and that was it. You have enough people with experience throughout the country that you can do the same thing. If someone wants to start doing this, it would be highly recommended they go spend one afternoon with someone who is experienced in this area. So I think it's actually a good analogy because it's a very similar type of device in many ways.

Dr. Mangel.

DR. MANGEL: Before we mandate too much, we

need to remember the drug is available on the market in the United States right now for other indications. I think the FDA should work with the company to provide as much educational material. Perhaps the company could work through AGA, ACG, et cetera to encourage the education of physicians. But it's available right now for anybody who wants to use it, and I think when we're framing our recommendation to the FDA on that, we also need to keep that in mind.

DR. WOLFE: I think FDA and the sponsor both get the idea. We want some kind of training. I feel comfortable with the two of them working it out.

Any other comments or questions?

(No response.)

DR. WOLFE: I want to thank all of you. It was an actually very delightful and lively discussion, and I also want to thank all of for the opportunity to spend the last couple of years as your chair. I really enjoyed the opportunity and the experience.

DR. HOUN: Thank you, Dr. Wolfe. Thank you so much.

(Applause.)

(Whereupon, at 3:02 p.m., the committee was adjourned.)