FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Wednesday, September 14, 2016

8:00 a.m. to 11:57 a.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Second Floor

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren D. Tesh, PharmD, BCPS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

Silver Spring, Maryland

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Bernard F. Cole, PhD

Professor

Department of Mathematics and Statistics

University of Vermont

Burlington, Vermont

Grzegorz S. Nowakowski, MD

Assistant Professor of Medicine

Mayo Clinic Rochester

Rochester, Minnesota

Vassiliki Papadimitrakopoulou, MD

Professor of Medicine

Thoracic/Head and Neck Medical Oncology

MD Anderson Cancer Center

Houston, Texas

Gregory J. Riely, MD, PhD

Associate Attending

Memorial Sloan Kettering Cancer Center

Associate Professor, Weill Cornell Medical College

New York, New York

Brian I. Rini, MD, FACP

Professor of Medicine

Cleveland Clinic Taussig Cancer Institute

Glickman Urological and Kidney Institute

Cleveland, Ohio

Bruce J. Roth, MD

(Chairperson)

Professor of Medicine

Division of Oncology

Washington University School of Medicine

St. Louis, Missouri

Thomas S. Uldrick, MD, MS

Clinical Director

HIV & AIDS Malignancy Branch, Center for Cancer Research

National Cancer Institute

Bethesda, Maryland

Phuong Khanh (P.K.) Morrow, MD, FACP

(Industry Representative)

Executive Medical Director, Amgen Oncology

Therapeutic Area Head, US Medical Organization

Thousand Oaks, California

TEMPORARY MEMBERS (Voting)

Karim Chamie, MD, MSHS

Assistant Professor of Urology

Department of Urology

University of California, Los Angeles

Los Angeles, California

Mark L. Gonzalgo, MD, PhD

Professor

Department of Urology

University of Miami Miller School of Medicine

Miami, Florida

Pamela J. Haylock, PhD, RN

(Acting Consumer Representative)

Adjunct Faculty, Sul Ross State University

Alpine, Texas

Oncology Nursing Educator

Medina, Texas

Brent Logan, PhD
Professor and Director
Division of Biostatistics
Medical College of Wisconsin
Milwaukee, Wisconsin

Patricia A. Spears
(Patient Representative)
Raleigh, North Carolina

Jennifer M. Taylor, MD, MPH
Assistant Professor, Urology
Baylor College of Medicine
Michael E. DeBakey VA Medical Center
Houston, Texas

John A. Taylor, III, MD, MS
Professor of Urology
Co-Director, Drug Development Discovery &
Experimental Therapeutics
University of Kansas Medical Center
Kansas City, Kansas

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD
Acting Director, Oncology Center of
Excellence (OCE), FDA
Director, Office of Hematology and Oncology
Products (OHOP)
Office of New Drugs (OND), CDER, FDA

Geoffrey Kim, MD
Director
Division of Oncology Products 1 (DOP1)
OHOP, OND, CDER, FDA

Ellen Maher, MD
Medical Team Leader
Genitourinary Cancers Team
DOP1, OHOP, OND, CDER, FDA

Gwynn Ison, MD
Medical Officer
DOP1, OHOP, OND, CDER, FDA

Chana Weinstock, MD

Medical Officer

Genitourinary Cancers Team

DOP1, OHOP, OND, CDER, FDA

Erik Bloomquist, PhD

Statistical Reviewer

Division of Biometrics V (DBV)

Office of Biometrics (OB)

Office of Translational Sciences (OTS)

CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. ROTH: Good morning, and welcome to the new venue. I'd like to first remind everyone to please silence your cell phones, smartphones, other devices, if you've not already done so. I'd also like to identify the FDA press contact, Angela Stark if she's here, back in the corner, for any comments, press-related comments.

I'd like to go around the table and have people introduce themselves. We have a number of new standing members, a number of one-time voting members. So if you just go around, let's start at this end of the table.

DR. MORROW: P.K. Morrow, medical oncologist. I'm at Amgen, Thousand Oaks.

DR. CHAMIE: Karim Chamie, urologist at UCLA.

DR. LOGAN: Brent Logan, biostatistician from the Medical College of Wisconsin.

DR. TAYLOR: John Taylor, a urologist at Kansas University Medical Center.

DR. TAYLOR: Jennifer Taylor, urologist at Baylor College of Medicine and the Houston VA.

DR. HAYLOCK: Pam Haylock, oncology nurse, and I'm the consumer representative.

MS. SPEERS: I'm Patty Speers, the patient representative from Raleigh, North Carolina.

DR. ULDRICK: Thomas Uldrick, medical oncologist, Center for Cancer Research, NCI.

DR. RIELY: I'm Greg Riely, a medical oncologist from Memorial Sloan Kettering.

DR. RINI: I'm Brian Rini, a GU-medical oncologist from Cleveland Clinic.

DR. ROTH: I'm Bruce Roth, a GU-medical oncologist from Washington University in St. Louis.

DR. TESH: Lauren Tesh, designated federal officer, ODAC.

DR. COLE: Bernard Cole, biostatistics, University of Vermont.

DR. PAPADIMITRAKOPOULOU: Vali Papadimitrakopoulou, medical oncologist,

MD Anderson.

DR. NOWAKOWSKI: Greg Nowakowski, medical oncologist, Mayo Clinic, Rochester.

DR. GONZALGO: Mark Gonzalgo, urologist from University of Miami.

DR. BLOOMQUIST: Erik Bloomquist, a statistician for FDA.

DR. WEINSTOCK: Chana Weinstock, medical officer, FDA.

DR. ISON: Gwynn Ison, medical officer, FDA.

DR. MAHER: Ellen Maher, oncologist, FDA.

DR. KIM: Geoff Kim, director, Division of Oncology Products I, FDA.

DR. PAZDUR: Richard Pazdur, office director.

DR. ROTH: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without

interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in only the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks. Thank you.

Now I'll pass it off to Dr. Lauren Tesh who will read the conflict of interest statement.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs

Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special

government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meetings, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of new drug application 208714 apaziquone for intravesical instillation, application submitted by Spectrum Pharmaceuticals, Inc. The proposed indication for this product is for the immediate intravesical

instillation post-transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer. This is a particular matters meeting during which specific matters related to apaziquone will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. P.K. Morrow is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by this speaker is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Seth Lerner has acknowledged several contracts and/or grants involvement as an investigator, and consulting activities with various pharmaceutical firms regarding bladder cancer, including non-muscle invasive bladder cancer.

These interests include involvement with the Southwest Oncology Group, and as a site investigator of Spectrum Pharmaceuticals phase 1 clinical trial of apaziquone. As a guest speaker, Dr. Lerner will not participate in committee deliberations, nor will he vote.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a

personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ROTH: Thank you. We'll proceed with some opening remarks from the agency presented by Dr. Chana Weinstock.

Opening Remarks - Chana Weinstock

DR. WEINSTOCK: Thank you, Dr. Roth.

Members of the advisory committee, colleagues, ladies and gentlemen, my name is Chana Weinstock, and I'm going to outline the agency's concerns with the apaziquone new drug application, or NDA.

The agency recognizes that non-muscle invasive bladder cancer is an area in which drug development has historically been difficult and in which there have been no recent drug approvals. We remain committed to working with industry to

develop effective new drugs in this area.

Shown here is the trial design for two large, randomized, placebo-controlled trials of apaziquone, a drug chemically related to mitomycin. Apaziquone was used as a single intravesical instillation post-transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer.

The primary analysis population is shown of patients with stage 2A, grades 1 to 2 tumors, by central pathology review, with the caveat that at the time of instillation, results of central pathology review were not yet available to each investigator. The primary endpoint was recurrence rate at two years.

The regulatory background of apaziquone is as follows. In 2007, a Special Protocol Assessment Agreement, or SPA, was given by the division for a trial of a single instillation of intravesical apaziquone following TURBT. Sample size and trial endpoints were agreed upon between the applicant and the FDA. A second study was designed to be

almost identical to the study under SPA. Both studies failed to meet their primary endpoint of an improvement in 2-year recurrence.

In December 2012, the applicant presented a pooled analysis of the two trials that showed an approximately 6 percent decrease in the 2-year recurrence rate of bladder cancer on the apaziquone versus the placebo arms, and proposed to use these data to support an NDA submission.

The FDA informed the applicant that since the pooling was not prespecified, it would not be acceptable to support an approval. The FDA advised the applicant not to submit an NDA, and that if they did, a public ODAC discussion would be required.

The sponsor submitted their NDA three years later, in December 2015. The division agreed to file the application, but reiterated that nothing had changed in terms of the acceptability of these data, and that a public ODAC discussion would be required, which is the purpose of our gathering today.

So when reviewing data submitted such as these, what are the statutory requirements guiding FDA decision-making related to drug approval? Statutory obligations require us to look for substantial evidence that a treatment effect has been identified, and is not due to variability in the underlying disease, bias, or chance alone.

This treatment effect is generally demonstrated through well-controlled, and well-conducted investigations. By law, sound evidence of effectiveness is a crucial component of the agency's benefit-risk assessment of a new product, otherwise we could be in danger of essentially approving a placebo.

In light of this, we present two major issues for the committee to consider. First regarding efficacy, is there substantial evidence of a treatment effect demonstrated in the data presented?

There are several reasons we question whether substantial evidence of efficacy has been demonstrated. Trial 611 and 612 both failed to

meet their primary efficacy objectives. The confidence interval around the observed approximately 6 percent difference between arms did not exclude zero, meaning that we cannot rule out the possibility that the effect of apaziquone is less than that of placebo.

The post hoc pooling strategy used to obtain a nominal p-value is problematic, as this was not adopted prospectively, and there is a danger that the observed approximately 6 percent difference between arms could be due to chance alone.

The post hoc subgroup analysis that attempted to demonstrate an optimized instillation time of greater than 30 minutes post-procedure is considered hypothesis-generating only. There is enough missing data in each study at the 2-year cystoscopy mark to lead to an approximately 20 percent overall rate of missing data, which is greater than the approximately 6 percent difference in 2-year recurrence rate between arms. This brings into question the reliability of the 6 percent difference, and would also be expected to

affect secondary trial endpoints, such as time to recurrence.

The second major question to consider, if and only if you do think that a substantial evidence of a treatment effect has been demonstrated, is this effect clinically meaningful?

The approximately 6 percent difference in 2-year recurrence between arms is smaller than expected. It is smaller than the 12 percent difference used by the applicant in their original sample size calculations, and it is smaller than the 14 percent difference in the 5-year recurrence rate seen with the use of available intravesicular therapy in the most recent meta-analysis.

Additionally, to put into context the kind of recurrence that was actually decreased, in these trials recurrence was defined as any histologically confirmed bladder cancer. Most recurrent disease was low grade, non-muscle invasive disease. This could potentially translate into fewer transurethral resections, but would still require extensive follow-up cystoscopy. Few patients

progressed to muscle invasive disease in the 2-year treatment period.

These are the two major questions we would like the committee to consider when reviewing the applicant's data.

To review, as the committee is presented with analyses of the submitted data, we ask for advice in evaluating the following. Please consider if substantial evidence of a treatment effect has been demonstrated. Two trials have failed to meet their primary endpoint. Strategies attempting to salvage these data by pooling two studies or by focusing on subgroup analyses are problematic.

Missing data further cast doubt on the reliability of the point estimate of efficacy. If you do think an effect has been demonstrated, please also consider the clinical meaning of this effect, given the fact that it was less than expected and less than literature reports of effectiveness of available therapy, and that primarily low-grade disease was prevented.

We would also like to note that there is an ongoing trial of apaziquone in non-muscle invasive bladder cancer that has been designed to address some of the hypotheses generated from study 611 and 612, including time to instillation. We await these results as well, and hope that they will demonstrate substantial evidence of a clinically meaningful effect. Thank you.

DR. ROTH: Thank you, Dr. Weinstock. We'll move on now to our guest speaker presentation from Dr. Seth Lerner.

Presentation - Seth Lerner

DR. LERNER: Thank you, Dr. Roth.

It's a real privilege to be able to spend a morning with you and observing this process. And let me just tell you a little bit about me. I've spent the better part of my 24-year career to date embedded in this disease, so I inherently do have some biases in that respect. These are the specific financial disclosures that were already discussed.

I also want to mention that I'm the local

bladder committee chair for the Southwest Oncology Group, and we have a clinical trial, 0337, in this space. It's a randomized trial of intravesical saline versus gemcitabine. And that trial has been completed but not reported yet. And as a strong patient advocate, it's hard to get away from those intellectual and clinical biases.

I was asked to provide a bit of an overview of bladder cancer. This is what I'll try to cover. The original request was a 20-minute talk, and then I looked at the agenda on Monday and saw that it was 15 minutes. So I'll try to get through the slides, and you obviously have those for your own use and review.

Bladder cancer is a very common disease. It's the 4th most common cancer in men in this country. It's the 10th most common solid tumor malignancy in women. The incidence over the last couple of decades has increased significantly, in part because of increased detection of probably low-risk disease, and a bit of reclassification issues. Mortality has increased a bit over time,

but still patients are living quite a long time in terms of current SEER statistics.

It's a disease of elderly patients particularly, and the prevalence is really the big issue because so many of these patients are living with particularly non-muscle invasive bladder cancer, which imposes a very high burden of both treatment and surveillance, and it's the most expensive cancer from diagnosis until death, and these statistics have been well-known for quite some time. So it represents a huge unmet need.

Because, in this particular case, these trials, as I understand it, were conducted in both U.S., Canada, and Poland, I was asked to give some statistics. And I reached out to a good friend of mine, Roman Sosnowski, who's a urologic oncologist in Poland. He provided these data for me.

If you look on the left side of the curve, you'll see that bladder cancer is the fourth most common cancer in men in Poland as well, perhaps not quite as common in women as it doesn't make the top listing here on the right. And he also indicated

that they follow the EAU guidelines, which I'm going to present in just a couple of slides.

This is a schematic of staging, the T staging in bladder cancer. So the most common, about 75 percent of these patients will have what's referred to as a non-muscle invasive bladder cancer, so carcinoma in situ. Not surprisingly, is a high-grade intraepithelial neoplasm that untreated has about a 50 percent probability of progression to muscle invasive bladder cancer over five years.

Ta is a papillary tumor confined to the epithelium. T1 is a papillary tumor that's invasive, usually high grade, but into the lamina propria only. And then T2, T3 and T4, what we call muscle invasive bladder cancer with increasing risk of lymph node and visceral and metastatic disease.

While this is a cystectomy series, it shows very nicely the 5-year survival probabilities based upon stage. And so you see that the non-muscle invasive group, and particularly those confined to the epithelium, death from bladder cancer, overall

survival is actually quite good. And as you get into more deeper levels of invasion, particularly T3, T4, higher probability of metastatic disease, these patients don't do as well long term.

There's been some changes, and I think it is relevant to the business that's being discussed today. So the grading system really changed in 1998. We historically used the WHO 1973 system. You can see it here, grade 1, grade 2, grade 3. And then in 1998 and then reaffirmed in 2004, the grading system changed to make it really easier for pathologists and easier for us as clinicians to identify the highest risk patients for progression to muscle invasive bladder cancer. So now we use a two-tier system, low grade, high grade.

Well how did that come about? So here's the 1973 system on the left, the current system on the right. And I can tell you that this has been reaffirmed in the most recent WHO publications from 2016.

So what happened was, particularly the grade 2 tumors were split into high grade, low

grade. About 60 percent of the grade 2 became low grade, 40 percent of the grade 2 became high grade. So grade 2 in the WHO 1973 system is really a mix of high grade/low grade. But if an error was made, it was to again help us identify the highest risk patients so that they could be treated appropriately.

This is a very reliable system for association with the most important outcome measures of recurrence and progression. So you see in the Kaplan-Meier plots, a very nice stratification comparing the two systems. So it's reliable. It gives us useful clinical information with respect to the most important endpoints.

There's a number of things that urologists must do in order to properly risk stratified patients and in order to determine the most appropriate therapy.

So what is a TURBT, a transurethral resection of a bladder tumor. It's done cystoscopically. And the most important things are to establish both grade and histology, and then

obviously to get as good an idea as we can about whether it's an invasive cancer or not.

All of our guidelines are imperative in taking a patient with a high-grade T1 tumor and mandating a second resection, typically 4 to 6 weeks after the first resection, in order to verify that there's either no residual cancer or no worse cancer, a muscle invasive cancer.

More recently, it's been called to our attention about certain variant histologies, micropapillary being the most common one, even though it's relatively uncommon, probably less than 10 percent of cases. This is a version of a high-grade cancer, a very aggressive high-grade cancer.

So micropapillary tells us that we're dealing with something more serious. We want to know whether it's a unifocal tumor or a multi-focal tumor. That affects the risk stratification. Is there a carcinoma in situ?

Then the most important probably time point is three months after the initial resection,

whether the patient has achieved a complete response or not, and that's associated with subsequent outcome. And then the last thing that we look at is tumor size stratification, typically about above or below 3 centimeters.

The European Association of Urology has had a longstanding history of risk stratifying based upon some of these features that I mentioned to you. The low-grade tumors fall in either low or intermediate risk, and that has to do with whether it's a solitary tumor, whether it's a first occurrence, and whether it's above or below 3 centimeters.

High and very high risk is any high-grade cancer. So anything that's high-grade, Ta or T1, carcinoma in situ, and certainly muscle invasive cancer -- well, we're talking about non-muscle invasive -- falls into that category. Intermediate risk is everything in between.

So these are the multi-focal, recurrent Ta, low-grade tumors. And these make up roughly about a third of the patients, but when you combine the

low-risk patients, that's really the majority of patients who present initially.

The AUA and SUO have published their guidelines. These were available online just a couple of months ago. And while they are mostly similar, some of the Ta high grade, the small Ta high-grade tumors fall into the intermediate risk category. And you'll see that this is relevant to the treatment space of perioperative chemotherapy.

This is a commonly used risk calculator that was developed by the EORTC, and it stratifies patients based upon risk group and their probability of recurrence and progression. This was based largely on intravesical chemotherapy trials, and I think that's very important to remember. And you can see that in particularly intermediate and high-risk patients have -- this risk stratification is primarily relevant to the risk of progression to a more aggressive, potentially invasive cancer.

This is a slide that I use quite frequently because it's easy to remember the treatment

algorithm. So if you have a low-risk patient, the first occurrence of a Ta low grade, 3 centimeters or less, perioperative chemotherapy, single dose chemotherapy would be the appropriate choice in that patient.

Intermediate risk, they're going to get peri-op plus typically, induction intravesical chemotherapy with or without maintenance. And now we know that BCG can also be effective in these patients.

Then the high-risk patients are going to get induction BCG plus maintenance therapy out to three years. This very high-risk category is something that the EAU has recently re-clarified, reclassified if you will. And these are the highest risk patients, and frequently radical cystectomy is the most appropriate treatment for them as an early intervention.

I think that this group knows these data quite well, and I put this up here to show the current approved drugs and the current spaces in which they are approved, according to the label.

BCG obviously has been around for quite some time.

Thiotepa is an older drug that we don't use really much or any, at all, because of some of the features of the drug in terms of absorption. Then, as you know, valrubicin was approved for BCG refractory carcinoma in situ, and that approval was in 1998. So we've had no new intravesical therapy approved since that time.

What I did here is I pooled the guidelines, a number of the guidelines that are in use today together. AUA is the American Urological Association, just published, or just revised and updated this summer; the NCCN guidelines, which are very commonly used; and the European Association of Urology. CUA is the Canadian guidelines, and then NICE is a UK guidelines.

For the most part, they're relatively harmonious, and I think that there's only some variability really with the intermediate risk patients.

There's some data to suggest that following induction chemotherapy for an intermediate risk

patient, that monthly maintenance out to a year will help reduce the recurrence rate. For intermediate risk, BCG plus one year of maintenance. There's a big study done by the EORTC. And then, as I mentioned, for the high-risk patients, they're going to get three years of maintenance.

Cystectomy would be reserved up front for only those very high-risk patients, or patients who progress or recur with a high-grade tumor after intravesical BCG, and BCG unresponsive disease.

The FDA has been very responsive to the needs of our community, and I cite three publications here, which, the first one was a joint effort by the AUA and the FDA, a very important meeting that occurred in 2013, and the report was published in 2014.

This was really designed to clarify what the expert community and the FDA experts felt about the highest risk patients, BCG unresponsive disease, and led to the idea that it would be acceptable to do a single-arm trial, registration trial, in a

disease space for which there really was no appropriate comparator, notwithstanding that valrubicin had been approved for that space in 1998.

We were then asked by Jonathon Jarow to come together. About five or six of us met and came up with a clarification of disease states. That was published in Bladder Cancer. Then more recently a white paper originated from the FDA was published in Bladder Cancer in 2015.

So there's been a lot of very important crosstalk between the expert community and the FDA, and I think this has really helped quite a bit in terms of clarifying disease states and then pathways for registration.

Briefly here's a case, 60-year-old woman, gross painless hematuria for six months, multiple courses of antibiotics, which unfortunately is quite common. Before the patient gets to a urologist for evaluation, she has a typical low-grade Ta tumor. We would classify this as low risk, first occurrence, less than 3 centimeters.

And the most appropriate therapy for her is a perioperative dose of intravesical chemotherapy.

These are the drugs that are currently available. Epirubicin is really not used so much in this country as opposed to Europe. The drug is retained typically for about an hour. And one can do this within the operating room, right after the completion of the operation, or within a few hours, and in some studies up to 24 hours. Some studies would suggest that it needs to be done within 6 hours.

We don't use, in the setting of perforation, mitomycin, as you'll see in a minute. If it gets into the soft tissue around the bladder because of the perforation, it can cause necrosis, and this can be fairly devastating. BCG has a lot of attenuated bacteria, is never used in this setting.

I mentioned epirubicin. This was an important study that was conducted in Sweden. It was a randomized trial of single-dose intravesical epirubicin versus no treatment. And what you can see that there was a statistically significant

improvement in recurrence-free survival in primary tumors, single tumors, but not in recurrent tumors or multiple tumors. And I think this is one of the issues that sort of plague urology, is trying to figure out do we give it to everybody, or do we give it to just the lowest risk patients.

There are some rare toxicities. The CT scan on the left is an example of what I mentioned about mitomycin C getting into the soft tissues and causing necrosis. And you see a lot of dystrophic calcification, and this can actually be quite devastating, take months or even longer to recover from.

I think all of us have seen patients that end up with a cystectomy. But, having said that, these are rare events. You can see an ulcer in the buccal mucosa coming from use of gemcitabine as well.

There are two important meta-analyses that have been recently published. This one that was published in 2013 shows a 38 percent relative risk reduction. These are all randomized clinical

trials using different drugs.

Then Richard Sylvester published an individual patient data analysis in 2016 from 11 of 13 trials, very large number of patients. Relative risk of reduction again, you see 35 percent, with a hazard ratio of 0.65. And I think most importantly, the 5-year recurrence probability reduced from 59 percent to 45 percent.

So as a class, and as a disease space, peri-operative chemotherapy seems to have a beneficial effect on reduction of recurrence probability.

This is the Kaplan-Meier plot from the individual patient meta-analysis. And as I mentioned as part of disclosure, but also to understand what else is going on in this space, that intravesical gemcitabine has been tested in a randomized trial by the Southwest Oncology Group, and the primary endpoint will be reported actually quite shortly.

Just to wrap it up, I was also asked to comment about utilization. As I think most of the

urologists are well aware, that there's a lot of data suggesting that even though we have level 1 evidence from a number of different clinical trials, a number of different drugs supporting the use of this, the utilization across the continent is really not perhaps where we would like it to be.

This is a survey published by Mike Cookson in 2012 showing that only 17 percent of patients receive peri-operative instillation. And I think Dave Miller and the group at Michigan have really called our attention and coined a term called "judicious use."

I think it's really important to remember that it's not 100 percent of patients that should be getting this treatment. The concept of judicious use says, well, who shouldn't get it, and then who should get it. And then amongst those, how many get it.

This is a huge collaborative project across five states that the group has worked with. So they've suggested that the ideal use is somewhere between a third and 40 percent. And in their

study, the vast majority of patients did get appropriate and judicious use of intravesical chemotherapy.

So it's not a one size fits all, and it does require some careful thought and case-by-case determination of the appropriate utilization.

In Europe, I think similar issues have been described. But you can see from this study by Juan Palou report in 2014, that 43 percent received peri-operative chemotherapy. There were some variations between countries, the training of the urologists in terms of their education and knowledge, and then some various aspects of risk assessment.

In Canada, there's not really any data. I reached out to Peter Black and Wes Kassouf, two colleagues, urologic oncologists, experts in bladder cancer. And they provided me with a number of off-the-cuff reasons, if you will, for low utilization in Canada as well.

In summary, it appears that low and intermediate risk patients would be the most

appropriate ones for consideration of this. Just as a reminder, low risk is the solitary Ta low-grade tumor less than 3 centimeters, first occurrence. Intermediate risk is going to be multi-focal, larger, or recurrent tumors. And despite these rare toxicities, the drugs in use today, particularly mitomycin, are I would say relatively safe.

Just a comment about mitomycin is that there have been times when we cannot get the drug. And when we can get it, it has to be compounded, and in my center that's been as much as $1600 a dose. So I would say that there's a large unmet need for clinical trials in this space and drug development, and hopefully at some point in time, drug approval.

Utilization varies, and there are some geographic differences. But our guidelines are very consistent in terms of their recommendations for use. So I'll conclude there. And again, I want to thank you very much for the opportunity to be with you today.

DR. ROTH: Thank you, Dr. Lerner.

If there are questions, we're going to wait until after all the presentations are made. We'll move on to the applicant's presentation.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, the FDA believes that it's important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this

issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We'll now proceed with the applicant presentations.

Applicant Presentation - Anil Hiteshi

DR. HITESHI: Thank you, Dr. Roth, and thank you Dr. Seth Lerner for the excellent overview.

Good morning. I'm Anil Hiteshi, head of regulatory affairs. I would like to thank the FDA and the advisory committee members for your time today.

Apaziquone is also known as Qapzola, EOquin and EO9. Spectrum has been working with FDA and leaders in urology for over 14 years in developing apaziquone, which can provide treatment options in non-muscle invasive bladder cancer by reducing the risk of tumor recurrences and related complications.

We will address the question before you regarding substantial evidence of treatment effect, as well as the excellent safety profile of

apaziquone to support the approval at this time.

Shown here is the proposed indication and dosing recommendation for apaziquone. We have narrowed the indication slightly from that in our briefing book to reflect the studied population, patients with low and intermediate risk, non-muscle invasive bladder cancer.

We will summarize the results from adequate and well-controlled studies that form the basis of substantial evidence of efficacy. Together with our clinical experts and investigators, we will discuss the clinical benefit of apaziquone and its advantages over currently available treatments.

We are asking you today to consider voting in favor of apaziquone, which has a clear, positive impact on patients.

Apaziquone has demonstrated strong anti-tumor activity in two marker lesion studies, and in the largest clinical development program that has been undertaken in non-muscle invasive bladder cancer involving over 1800 patients. The positive benefit-risk profile of a single

4-milligram dose of apaziquone instilled in bladders soon after surgery can fill the large unmet medical need in this patient population.

Here is the list of presenters. We have with us today four of the investigators who have been involved in the development of apaziquone and have participated in the clinical studies. They are leading clinical experts in urology community and treat bladder cancer patients every day. Spectrum has paid for their travel expenses and/or consulting fees. They do not have any financial interest in the outcome of this meeting.

I would now like to invite Dr. Shore to the podium. Thank you.

Applicant Presentation - Neal Shore

DR. SHORE: Thank you very much.

Good morning, ladies and gentlemen. I am honored and privileged to have the opportunity to share with you my perspective on the medical need for immediate post-operative intravesical chemotherapy for patients with low and intermediate risk bladder cancer who have undergone tumor

resection.

As Dr. Lerner pointed out, bladder cancer has a very high incidence and prevalence within the United States. The vast majority of these patients have non-muscle invasive bladder cancer. The disease predominately afflicts older patients. This patient population faces other significant comorbid conditions, notably correlated to tobacco use, resulting oftentimes in significant cardiopulmonary disease.

Bladder cancer has the highest recurrence rates of any cancer. With approximately 600,000 cases in the United States, there is a long-term requirement for tumor surveillance. Repetitive rigid cystoscopy transurethral resection, or TUR, increases the risk of associated morbidities for patients, as well as additional significant healthcare costs. As has been stated, bladder cancer is the most expensive cancer to treat per capita in the United States.

The bladder cancer stratification has already been clearly stated. Our presentation

today is focused on Ta G1-G2 tumors, the majority of the presentation of bladder cancer patients, and these are categorized as low to intermediate risk.

This slide demonstrates for you, from the Bladder Cancer Advocacy Network's site, to the left is a flexible cystoscopy. It's the diameter, oftentimes smaller than a Foley catheter. It's malleable, and we use this for surveillance and monitoring. We don't use this for biopsy and resection.

To the right, you see a rigid steel cystoscope, which I'm going to show you a video in a second, which is a full-on surgical procedure with anesthesia in order to resect the tumor.

Here's a video from my center done approximately two weeks ago. This is a typical patient's day. It takes an entire day to have this done. They have to come in, register. They have general anesthesia or spinal anesthesia. They're in an operating room. They're in stirrups in a lithotomy position, fully draped and prepped.

This is a flexible cystoscope just for

demonstration purposes, small and malleable. This is a rigid cystoscope. It's made of steel. This has to be intubated into the urethra. It goes through the male or the female urethra. And you'll see in a second, here's a video to the left, navigating the urethra to ensure no injury to the urethra, which can occur.

Then ultimately on a camera, you're going to see the resecting loop. This is a high intensity, heat-wave loop that will resect the tumor. You can see the intense firing of the loop resecting the tumor down to muscle. One can see that this can incur bleeding, perforation, if not done correctly.

So this is not a minor procedure and has certain clear, obvious risks associated with it, but this is the standard of care for resecting bladder tumor, whether it be superficial Ta G1-G2 or muscle invasive tumor.

The patient is undergoing this procedure, and on conclusion of the procedure, you'll see we have to irrigate out. So the irrigation procedure is to remove all of the tumor. And at the same

time, while there's irrigation going on, we also are controlling bleeding.

Now as the tumor is collected and irrigation is being performed, there's now a potential for not only removal macroscopically, but also microscopically of tumor. Some of this tumor can be implanted. So there are flotation cells, or the concept of flotation, which could lead to impregnation of tumor.

This next video will show you schematically again what happens. Look at the Ta tumors. Now there's many of them there. It's certainly possible that we could miss resecting these tumors, and we think we've completed but we might have left one high up in the dome or on the left or right side.

Now there are all these fragments of tumor floating around, so there's a real significant risk of missed tumors and also for implantation of tumor afterwards if we don't instill a therapy to reduce recurrence. Thus, the reason and the main indication for why we did this trial.

As has been already stated, the international guidelines clearly, virtually unanimously suggest that a single post-operative chemotherapy is appropriate for low-risk tumors. But the real question is, are these guidelines really being followed?

Now this paper was shown by Dr. Lerner, and first author Mike Cookson, chairman of urology at University of Oklahoma, and Sam Cheng, second author, now chairman of the Bladder Cancer Guideline Committee.

The survey clearly illustrates, of over 260 urologists, both academic and community, that regarding the use of immediate post-operative chemotherapy, there really is a paucity of use. The survey showed only 2 percent of these urologists surveyed used it all the time, and 67 percent never used any form of IPOC therapy.

So why do we see this rather gross underutilization? Well, the FDA's briefing document suggests that it may be due to a perceived low efficacy of current treatments. I would say

that's a variable, but not the main variable.

In peer reviewed publications, the reasons most commonly reported by the urologists included fear of an unrecognized bladder perforation and associated medication complications; reluctance by the staff to handle therapies not approved for intravesical use, or prepared for intravesical use; mixing and instilling cytotoxic agents; the logistics of ordering in the hospital setting; lack of reimbursement without approved labeling; and most importantly, again emphasize most importantly for the clinician was the toxicity concern.

What are these reported toxicities with a single instillation of mitomycin C? Even with the underutilization of IPOC, mitomycin is still considered the most commonly used therapy for low-risk NMIBC in the United States. That said, up to 41 percent of patients treated with mitomycin will show chemical cystitis. This is described as a manifesting dysuria, burning upon urination, frequency, urgency, suprapubic pain, and pelvic discomfort.

As was mentioned by Dr. Lerner, there can result in poorly healing chronic calcifications of post-MMC with one instillation. It's been very well documented, and can result in delayed wound healing, urinary dysfunction, persistent urinary infection, and decreased bladder capacity.

The unrecognized bladder perforation during TURBT with a subsequent post-op instillation of MMC can result in extravasation with perivesical inflammation and a chemical peritonitis.

I'm showing you here the rather unfortunate case of a 77-year-old man who had one single instillation of MMC post-TURBT for a Ta G2 tumor, which ultimately led to a persistent fistula and a cystectomy. There have been numerous reports of this in the urologic literature.

What is the efficacy of post-operative chemotherapy? The meta-analyses by Dr. Richard Sylvester have demonstrated a variable treatment effect. It should be noted that many of those studies used TUR alone as a control arm as opposed to a saline irrigation, as we did

consistently in the apaziquone studies.

TUR alone is not equivalent to placebo. It appears when placebo was used, the effect size was smaller. Moreover, it's recognized that TUR techniques have improved over the years, potentially narrowing the difference between treatment and control arms.

In fact a recent study by Di Stasi reported a more contemporaneous absolute reduction of 5 percent. And most recently, in 2016, an international bladder cancer group of key opinion leaders published and recommended that a 6 percent absolute reduction in recurrence rate is clinically meaningful. And this was published by Ashish Kamat of MD Anderson as the first author.

So what does a 6.7 percent reduction in recurrence really mean to my patients with NMIBC? Well, looking at the prevalence, it results in 20,000 transurethral resections under general anesthesia could be avoided per year; avoided per year.

Although complications after TURBT are not

typically severe in nature, but based upon the reported incidence of perforation and subsequent hospitalization after TURBT, we estimate that it avoids approximately a thousand bladder perforations and the requirement for possible hospitalization.

I'm here to present today that I find the data to be not only clinically of value, and valid, but of rather significant benefit to my patients. It's been my personal experience in doing multiple intravesical trials to date.

Thank you very much for your attention. I'd now like to invite Dr. Gajanan Bhat to present the efficacy and safety of apaziquone.

Applicant Presentation - Gajanan Bhat

DR. BHAT: Good morning. I am Gajanan Bhat. I will summarize the clinical development program, including efficacy and safety results of apaziquone.

Apaziquone is a fully synthetic bioreductive alkylating indoloquinone. The drug is activated by DT-diaphorase and other reductases. The drug is

active in both hypoxic and aerobic conditions. There is minimal systematic absorption after intravesical instillation. If it is exposed systemically, it is rapidly eliminated by the blood.

Apaziquone activity was tested in multiple bladder cancer cell lines, and compared with the activity of commonly used intravesical agents. As shown here, apaziquone is the most potent intravesical agent tested in vitro, which is 30 times more potent than mitomycin in bladder cancer cells.

A total of 1859 patients were studied in apaziquone clinical development program over 14 years. This is by far the largest program ever conducted to date in order to prevent tumor recurrence with post-operative instillation. We submitted our NDA in 2015.

Based on phase 1 study results, the 4-milligram dose was selected. In this study, 67 percent of the patients showed complete response. Also, in a phase 2 study, 46 percent of

patients with the Ta G1-G2 disease were dosed, and the doses were well tolerated.

Let me illustrate the anti-tumor activity using a pair of images from this phase 2 study with 46 patients. The image on the left is from baseline after TURBT but prior to treatment, leaving one lesion unresected. This is the marker lesion we are talking about.

On the right, the tumor has disappeared after instillation of apaziquone. And similar to the phase 1 study, this complete response is confirmed after biopsy was achieved in 67 percent of the patients. Thus, these two studies provided a strong safety profile and anti-tumor activity in marker lesion. This formed the basis for the pivotal clinical program.

Our two phase 3 studies are identical in study design except for one difference, that is exclusion criteria of number of tumors allowed. The details are in your briefing book. Then study 611 was designed under a special protocol assessment with FDA.

This was a global, multi-centered, double-blind, randomized, placebo-controlled, single-dose apaziquone studies. The timing of the instillation allowed in the protocols was between zero to 6 hours post-TURBT. Once dosed, patients were followed for 2 years for recurrence, assessed every 3 months using cystoscopy.

All tumor biopsies and specimens were reviewed by independent pathology conducted in a blinded fashion by Bostwick Laboratories to confirm the target patient population as well as recurrence. Patients once confirmed as the target Ta G1, G2 population did not receive any additional intravesicular therapy during the follow-up. Based on the literature at that time, each study was powered to detect 12 percent absolute difference between apaziquone and placebo.

Study with the analysis population, let me briefly summarize statistical methods. As shown in the previous slide, the target population in both studies were Ta G1-G2, as histologically confirmed by the independent review. This was the primary

analysis population for all efficacy endpoints. The remaining patients who were now confirmed to have Ta G1-G2 are included for the safety analysis.

The primary endpoint was a 2-year recurrence rate, as defined as a proportion of patients with recurrence on or before 2 years, as determined by independent pathology. A key secondary endpoint is time to recurrence. This is a very common endpoint in any oncology study. The time to recurrence was analyzed using Kaplan-Meier analysis and log-rank test.

The next few slides will summarize patient disposition and efficacy results. Patients were enrolled in over 150 study sites from three countries. The study 611 was a U.S. study. The majority of the patients in both studies were enrolled in U.S. as well as Canada, but mostly in the U.S. study sites.

Demographics, baseline characteristics, were similar between treatment groups and studies. The majority of patients in both studies were male, elderly, with grade 1/grade 2 disease.

In the next few slides I will summarize the primary and secondary efficacy data in Ta G1-G2 patient populations, starting with the primary endpoint to remind you the primary endpoint was a 2-year recurrence rate.

In study 611, which was a U.S. study, the relative reduction in recurrence for apaziquone or placebo was 15 percent, with an absolute difference of 6.7 percent and an odds ratio of 0.76.

In study 612, primarily conducted outside the U.S., there was a reproducible clinically meaningful relative reduction of 14.2 percent, with an absolute difference of 6.6 percent and an identical odds ratio of 0.76. Both of these studies did not meet a statistical criteria of significance, however integrated data from two studies provided the relative reduction of 14.7 percent, which was statistically significant.

The key point here is that between studies, although conducted in different countries and different regions, there was a remarkable consistency in the primary efficacy of recurrence

rate in two large studies.

Now, I will turn to a key secondary endpoint of time to recurrence, starting with study 611. The improvement in time to recurrence with apaziquone as presented using the hazard ratio was statistically significant in study 611. In study 612, although not statistically significant, a similar improvement was observed as seen from the hazard ratio.

The time to recurrence being an important endpoint in oncology studies, we have met statistical significance in one study and observed similar improvement in the other study.

Although not prespecified in the statistical analysis plan, Spectrum has performed a pooled analysis of efficacy, both simple and stratified, and the results of the recurrence rate and time to recurrence are provided here.

We believe this was justified as the studies were nearly identical in design, evaluable populations were identical, primary endpoint was the same, all study sites were in one of the three

countries, and essentially both studies started and ended at the same time.

As you can see from odds ratio from simple pooled and stratified pooled analysis, recurrence rate improvement met nominal p-value of less than 0.05. Similarly, the pooled analysis met nominal p-value of less than 0.05 for time-to-recurrence endpoint.

While the pivotal trial design was the subject of a special protocol assessment, it took a long time to put in place, as a trial design was challenging for both FDA and Spectrum. Some of the challenges included no precedence for study design as no regulatory type of studies were conducted in this indication. We needed to switch the primary endpoint to 2-year recurrence rate, as suggested by FDA, versus time to recurrence, which is commonly used in oncology.

We used meta-analysis data as the effect size to power the studies. This has significant heterogeneity in treatment effect based on literature available in 2004.

The effect with TURBT alone was not the same as placebo-controlled in these studies, as Dr. Shore mentioned. Thus, clinically relevant treatment effect of immediate intravesical therapy was not well understood for a 2-year recurrence endpoint at the time of the study design.

Nevertheless, why do we think our results are so convincing? It is because of the remarkable consistency and reproducibility of efficacy in two large, well-controlled studies, and in the majority of the subgroups of patients.

Our pivotal program provides the largest database of well-controlled studies. The estimated treatment effect is clinically meaningful in view of the recent literature data and development in this disease space.

We have performed several multivariate and subgroup analysis using demographics, baseline status, and time of instillations. The details are in your briefing book. As you see, with odds ratios from the forest plots of two studies, apaziquone demonstrated favorable treatment effect

in all subgroups with no considerable differences except for time of instillation. This includes primary versus recurrent, single versus multi-focal tumors, grade 1 versus grade 2.

However, since apaziquone is inactivated by blood, we looked at a time window threshold of at least 30 minutes post-TURBT to see any difference, as this is a typical time for hematuria to recede when a patient undergoes TURBT procedure.

In approximately 60 percent of the total patients enrolled in this time window, we have seen much higher efficacy in patients instilled at least 30 minutes post-TURBT.

Here is a summary of recurrence rate and time to recurrence in patients dosed at least 30 minutes after TURBT. The absolute difference in recurrence was consistent and was at least 10 percent in both studies, favoring apaziquone, with study 612 meeting nominal p-value of less than 0.05. Moreover, the time to recurrence was significantly improved in both studies.

Here are the Kaplan-Meier curves showing

significant improvement in time-to-recurrence data in two studies with nominal p-value of less than 0.05. These results are real. These are reproducible, consistent between two studies, and not hypothesis-generating. We propose apaziquone to be instilled at least 30 minutes after TURBT in our dosing recommendations.

In summary, apaziquone demonstrated strong anti-tumor activity from two early phase studies. We have two large well-controlled studies in phase 3 that form the largest database for any intravesical therapy.

We have demonstrated reproducible improvements in primary as well as secondary endpoint in two studies. The treatment effect is supported by recent recommendations of international bladder cancer group.

We have also shown that the efficacy is consistent across most patient subgroups. In particular, we have shown that 4-milligram apaziquone, when dosed at least 30 minutes after a TURBT, provides a much better efficacy with

significant time to recurrence improvement in both studies.

Overall, the data we presented from two studies provides substantial evidence of efficacy. We believe that the treatment effect we observed is not due to variability in the underlying disease, as we have shown in multiple subgroups of patients, and study bias, or due to chance alone.

Now, let's turn to a summary of safety from our apaziquone clinical development program. The safety data came from eight studies with 1859 patients enrolled, out of which 1,053 patients received apaziquone. The next slide summarizes the adverse events.

The rates of all AEs and treatment related AEs was similar between treatment groups as well as between studies. The treatment related AEs of grade 3 or higher were mostly less than 1 percent. Most AEs and SAEs occurred during the follow-up time. The most common treatment related AEs occurred primarily in genital urinary system organ class. The rates were less than 5 percent in both

groups and in both studies.

Overall, eight clinical studies conducted in NMIBC population with over 1800 patients shown a safety profile of apaziquone. The safety conclusion is that a single intravesical instillation of 4 milligrams of apaziquone post-TURBT was well tolerated, and the safety profile was indistinguishable from placebo.

In summary, the clinical program, including two large placebo-controlled pivotal studies, demonstrates consistent efficacy and provides substantial evidence of efficacy, and an excellent safety profile for treatment with apaziquone.

This concludes our data presentation. I would like to invite Dr. Fred Witjes to the podium. Thank you very much.

Applicant Presentation - Alfred Witjes

DR. WITJES: Thank you very much. Good morning to you all, Dr. Roth. My name is Fred Witjes. I am an oncological urologist from Nijmegen in the Netherlands. And with regard to bladder cancer, I am chairman of the Dutch and the

European bladder cancer guideline, and I have been chairing the WHO Ta T1 consensus meeting. And I'll try to put some of the information that you have now into clinical perspective.

The efficacy of apaziquone, I realize the trials were not significant, but what did we learn and what did we see in the last decade? We now have digital equipment, and we do a better bladder resection. So we have fewer recurrences, and there is therefore, of course, less recurrence between treatment arms.

I hope you realize that placebo treatment, like we did in this trial, where we do instill something in the bladder and take it out again, is not the same as no treatment where trials have compared instillation against a TUR only.

However, with regard to these trials, the results are consistent between both trials. The combined analysis is significant. There is significant increased time to recurrence if the drug is dosed after 30 minutes. And you've seen that currently these 6 percent should be considered

clinically relevant.

Is it an effective drug? It is effective. My team has done some of the initial studies, the phase 1 and phase 2 studies. We have done a marked lesion study. And as you see in the recent meta-analysis published in 2010, the highest complete response rate ever seen in a mark lesion study was found with apaziquone.

The marked lesion study is really studying efficacy of the drug. One tumor is left in place. You do your instillations, and then you see whether there's a complete response. That's totally different from the concept of preventing recurrences.

What about the below 30 minutes issue? I realize that sometimes that might be a logistic problem in U.S. hospitals, but I hope you realize that you've seen a video, and the effect of some bleeding on only 4 milligrams of apaziquone of course might be quite obvious.

Safety. It's important for my patients. Some of you are urologists and some of you are

oncologists. You know these patients. These are not very well patients. They're older. They are ex-smokers. They have cardiovascular disease, and they have pulmonary disease. So fortunately, apaziquone toxicity is a non-issue.

If you have a lethal disease, you might accept more toxicity. This is a non-lethal disease, so it is important that there is not toxicity.

What is present in the U.S. as alternative for an immediate instillation? Dr. Lerner already addressed that. Thiotepa registered in '59, that doesn't work for this indication as you can see on the left side in a meta-analysis. Mitomycin C, never been registered. It's potentially toxic, and there are some availability problems.

On the right side, the lower two slides, you'll see patients are treated last year. He had one instillation of mitomycin C. He had a fistula. He had a persistent fistula, shrunken bladder, and I had to take out his bladder; one of the reasons why I don't use mitomycin C anymore for this

indication. We use epirubicin in Europe. And BCG obviously is contraindicated in the direct post-operative setting.

Some more clinical arguments. Although it's in all guidelines, you've seen that, it is dramatically underused in the U.S. Dr. Chamie's present, and it's a very nasty example, but he has shown that in only 1 out of more than 4500 patients, all therapy and follow-up advice according to the guideline were followed.

Dr. Jarow has also stated only three drugs have been registered, so there is a large unmet need. And now there is a possibility to register a new drug for an unmet indication. And I really think this is also an opportunity for education of the urological community.

What's in it for my patients? The low-risk cohort is by far the largest cohort. In the U.S., it's 55 percent, with many, many recurrences and events. Though an intermediate risk is estimated to be 80 to 85 percent of prevalence, not incidence but prevalent bladder cancer, the overall

prevalence you've heard is around 600,000. Eighty to 90 percent is non-muscle invasive. Of those again, 80 percent is low to intermediate risk. And just imagine that you could reduce the recurrence rate to 6 or 7 percent of this cohort.

So what can I spare for my patients? Cystoscopies, because if I treat better, my follow-up doesn't have to be so strict. And for a urologist, the follow-up is something we do in 10 minutes. It's not very difficult. It's a flexible scope. But I have been on the other side of the scope, fortunately for a small bladder stone, but I can assure you, it's not a very pleasant experience.

What can I spare for my patients? TUR procedures, you've seen, it's a real operation and anesthesia. For the U.S., that might be reduction around 20,000 TUR procedures for the next year. So I think that's really relevant.

So my conclusion about the clinical benefit, yes, there is a reduction in the recurrence rate, and TURBT procedures, and follow-up cystoscopies.

It is very safe in this older patient population. And I think it is clinically relevant in 2016.

Thank you for your attention. I'd like to ask Dr. Mark Soloway to proceed.

Applicant Presentation - Mark Soloway

DR. SOLOWAY: Well, it's certainly a pleasure to be here. By way of apropos of Dr. Roth's initial comments, I'm receiving, my own design, no honorarium for being here. I believe in this subject, as you'll see.

I'm going to give some I think interesting historical perspective. First of all, for many of you who probably don't know me, I was fortunate to be the guidelines and editor of these two books on recommendations for bladder cancer by the International Consultation on Bladder Tumors, first in 2004 and again in 2011-12. And some of the people in this room were active participants in putting all these recommendations and the complete field of bladder cancer together.

These are the tumors we're talking about. Urologists are 90-95 percent very accurate in

saying these are Ta low-grade tumors. So that's not the issue. And again, just to emphasize, these are very, very common, by far the most common bladder tumors that we see.

These patients, again, rarely have a tumor, which is of higher grade. This is not a life threatening disease. And in fact, most subsequent tumors, whether you call them recurrences or new occurrences, tend to be very small. They are a nuisance problem, but an important one.

The natural history has been known for 40 years. And this is just one article I pulled up from 1978, long-term follow-up on this group of patients. And as you can see, these patients will rarely die of bladder cancer. That is not the issue. The issue is the subsequent tumors, which require treatment.

My unique perspective goes back to my days here in Washington and Bethesda. When I was a clinical fellow at the NCI, I was really luck to develop a bladder tumor model, which is, believe it

or not, still in effect today and still used in research labs.

Using a carcinogen, I was able to reproduce the human type, if you will, the same histology, the same essential biology in syngeneic mice. And in fact, I was fortunate to identify cisplatin at the time. It was an investigational drug. I went and presented my work, showing its effectiveness in the model to AACR. Alan Yagoda was there, and the rest is history. But amazingly, 40 years later, it is still the most effective drug in urothelial carcinoma.

Now, my next challenge was to think about why do we have such a high subsequent tumor rate. And because I developed this model, I had the opportunity to say, well, maybe we can figure out why. Certainly, it's the continued onslaught of the cigarette smoking or other carcinogen in the bladder, incomplete removal, but maybe implantation occurs. It was a hypothesis. So I had the opportunity to sort this out.

Using my model, first of all, I took the

mice, and I was able to simulate a "TUR," if you will, a little bit in quotes there. By cauterizing the urothelial super surface of the murine bladder, I was able to say, okay, I can alter the bladder surface.

Then what I did is I took my bladder tumor model syngeneic, I had the tumor line. So on the right, I cauterized the bladder, and of course no tumors developed by just cautery. On the left, I did not alter the surface of the bladder, and I put in the tumor cells. No tumors. But if I altered the surface of the bladder and put in the tumor cells, 80 percent of the mice then developed these tumors. So at least in this animal model, I proved an implantation occurs.

I then published this, and went on subsequent to publishing the fact that this occurs, the animal model. I then went on to talk about then putting in intravesical therapy into the bladder and showed, yes, you can prevent these tumors by immediate intravesical therapy.

So I said, well, we should go to the clinic

with this. Let's start using it in patients. And as you see, this is a publication, the rationale for doing this in 1980. Look how long it's taken to get some substance, or get people to use it, and still it's not an obvious thing and not commonly performed after all these years.

Again, you've heard this. I'll just go over it once more. The typical patient that I see, you have an elderly gentleman, your former cigarette smoker, comorbidities related to that. Very commonly, I can tell you in South Florida they're on anticoagulation.

So this patient comes in. He has hematuria. You do the flexible endoscopy in the office. You know it's a Ta low-grade tumor. So you plan a TURBT. But then there's a big step next. He's got to have medical clearance. He's got the anticoagulation, and then this potentially morbid operation, a TURBT performed.

It's not so easy. I just gave the first course at the AUA ever on how to do a proper TURBT, and the room was filled. This is not a simple

minor little operation like taking off a skin cancer by a dermatologist.

Now, it took until 1993 for the first large mitomycin prospective randomized trial to be done. So again, my research was in the late '70s, '80s, and it took about almost 15 years for the first study showing mitomycin. And in that study, importantly, one dose worked, less recurrences, but five doses were better. So the more doses you give, the better effect you're going to have.

The principle though is probably it does alter implantation likelihood. And as you've already heard over and over today, because of a good reason, it's a guideline. It's a guideline in EAU to give post-operative intravesical chemotherapy, and it's a guideline by the AUA and SUO as of 2016. And again, for good reason because it makes sense and it works.

If you look at this timeline starting in the '70s when we had thiotepa as an only agent, we then developed the animal model proving in principle that implementation is real. Urologists thought it

was, but this gave credence to that. Then you have the story with mitomycin C, which still is not used. I don't use it often because, honestly, I'm afraid of potential risk to the patient. I do use it quite frequently in the office where I'm just cauterizing tumors.

You then have the European studies, but very few, if you'll note over the last 20 years, have been done until this apaziquone study in the United States.

So again, we're talking about a broad range of patients. One of the things I think we should highlight is the low and intermediate risk, they're basically biologically the same, the low-grade Ta tumors, except for the bottom two categories. So it's a large group of patients that would be influenced by proper intravesical chemotherapy post-TURBT.

BCG, as far as I'm concerned, for the low-grade Ta, you should throw out the window. I'm being a little bit harsh. First of all, you of course cannot give it immediately after surgery.

It's not going to alter implantation. I think it's way over utilized for the low-grade Ta. And personally, and actually Ashish Kamat just wrote a paper on this, I don't think it works very well at all for this large population.

For the low-grade papillary, BCG doesn't work well. It works very well, it's a game changer for CIS and high-grade T1 post-TURBT, if you do a complete TURBT, to alter CIS in the bladder. But for low-grade Ta, the ones we're talking about, BCG simply does not work very well. It's not an alternative.

Why apaziquone? Why am I here? Why am I supporting this? I do believe FDA approval for a drug would be very useful. This is a very safe drug. I was involved in the trials, that's not an issue. And it was effective; my interpretation, it is effective. Maybe not as good as we would have liked, but it is effective. It decreases the subsequent chance that this elderly man will have another TURBT. And remember, this is only a single dose. You can only ask so much of a single

post-operative intravesical chemotherapy application.

So if we wait for the next study, that means five, six, seven years before my patients have the alternative to have this agent and prevent some of these procedures.

I honestly think it's going to improve utilization. Mitomycin simply is not used. It's fine. It could be used, and I use it sometimes, but you've already heard Fred Witjes, they don't even use it anymore.

So we can reduce the morbidity of the TURBT. The surveillance endoscopies will continue, but a little wider intervals. If the patient doesn't have a recurrence, then you break that over time.

So it's a pleasure to be here. I'm honored to do so, and I will call Dr. Raj.

Applicant Presentation - Rajesh Shrotriya

DR. SHROTRIYA: Thank you, Dr. Soloway.

Good morning. I am Dr. Raj Shrotriya, chairman and CEO of Spectrum Pharmaceuticals. I would like to thank the FDA and the advisory

committee members for their time today, and the opportunity given to us to share the results of our apaziquone development program, which has been underway for more than 14 years. During this time, we have worked closely with the FDA, top thought leaders and bladder cancer experts throughout the world.

The current therapeutic landscape has remained essentially stagnant for nearly 50 years. As you just heard from Dr. Soloway, not much progress has been made. There are no FDA approved drugs for low or intermediate risk non-muscle invasive bladder cancer. Due to serious toxicities, off-label drugs are rarely used by urologists in this country.

We have presented to you the data from a large, international clinical development program involving more than 1800 patients. This is the largest clinical study database in this patient population for whom the prospect of tumor recurrence and additional treatment is a source of great anxiety. What the clinical urologists have

demonstrated today is a clear unmet medical need.

Please consider three significant points today. Number one, for low-risk bladder cancer, the goal of therapy is to reduce visits to the operating room by these elderly, fragile patient populations who have morbidities such as COPD and cardiovascular diseases. Apaziquone is extremely safe, as our first obligation to patients is to do no harm.

Number three, apaziquone demonstrated a consistent, clinically meaningful treatment effect in two large randomized, placebo-controlled studies, 611, 612, especially when you look at time to recurrence, which is the standard way of looking at drugs like time to event.

Apaziquone will provide physicians and patients alike with a new, safe and effective treatment option that would help reduce the number of TURBTs in a largely older, fragile patient population. This means fewer patients will face invasive, painful TURBT procedures and the associated complications. In addition, a reduction

in TURBT procedures will directly translate to reduction in cost to the healthcare system.

We believe apaziquone would fill an unmet medical need for a safe and effective agent. It would meet the various guideline recommendations for post-op intravesical, single-dose chemotherapy.

Please bear in mind that apaziquone is administered in a small 4-milligram, single dose, that is instilled through an existing catheter and kept in the bladder only for 60 minutes. This spares patients multiple visits to the operating room.

Apaziquone is not about the survival benefit, as is the case in most cancer patients. The issue here is recurrence or lapse of tumors that requires repeated transurethral resections.

As you discuss the FDA question before you, please consider the totality of the information provided today. The data presented is not due to variability in the underlying disease, bias, or chance alone. We believe the data for apaziquone does meet the statutory requirements and provides

substantial evidence of safety and efficacy.

We hope you will vote in favor of apaziquone for the benefit of those bladder cancer patients who are suffering, and have been suffering, and will continue to suffer if apaziquone is denied approval today. Thank you.

DR. ROTH: My thanks to the presenters for the applicant. We'll move on the FDA presentations.

FDA Presentation - Gwynn Ison

DR. ISON: Thank you, members of the advisory committee, colleagues, ladies and gentlemen. My name is Gwynn Ison, and I'm going to present the clinical portion of the FDA analysis of the apaziquone NDA. My presentation will be followed by the FDA's statistical analysis by Dr. Bloomquist, and then I will provide a brief safety analysis and discuss our conclusions. The members of the FDA review team are shown on this slide.

The proposed indication, which has been mentioned, is apaziquone, is a bioreductive

alkylating indoloquinone, indicated for immediate intravesical instillation post-transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer. I will remind the audience that apaziquone is a chemical analogue of mitomycin.

The main issues for discussion with regard to this application are shown here. First, we ask the committee to consider if the applicant has demonstrated substantial evidence of the efficacy of apaziquone, which is also to say, can we establish, from the data presented, whether there is any difference between apaziquone and placebo.

Second, only if there is substantial evidence of a treatment effect for apaziquone do we ask the committee to discuss whether the effect is clinically meaningful.

We want to remind the committee that the specific tumors addressed in the current application include non-invasive Ta lesions of low and intermediate histologic grade 1 to 2. The natural history of these low-risk tumors, which has

been discussed, is that they do have a tendency to recur, but they are typically low grade at the time of recurrence, and these types of tumors rarely progress to muscle invasive cancers.

This risk of progression is estimated to be 0.2 percent at one year, and 0.8 percent at five years, according to the EORTC risk tables. These risk tables are often used by clinicians to predict recurrence and progression risk in individual patients.

We will note that not all patients on the two trials in the current application fell into the very lowest risk group at baseline given all of the variables considered. The estimate of the risk of recurrence I've given truly represents the very lowest risk patient who could have been enrolled in either trial.

Finally, we point out that in practice, all patients diagnosed with these types of bladder tumors are followed for evidence of recurrence or progression with cystoscopy at regular intervals.

This is again to show what the guidelines

are from the different expert panels on the management of low-grade non-muscle invasive bladder cancer, including the NCCN, the American Urologic Association, and the European Association of Urology.

All sources recommend transurethral resection of bladder tumor. Depending on the source, the use of a single dose of intravesical chemotherapy should be considered or is recommended. The most typical agent used is mitomycin.

These expert guidelines are based on a series of meta-analyses. The most recent meta-analysis shown in this slide was published in the European Journal of Urology in 2016, and included 13 trials, 11 of which had individual patient data available on 2200 patients. The median duration of follow-up in the patients included was six years for recurrence and nine years for survival.

The table provides the breakdown of treatment effect by agent. The meta-analysis

included randomized controlled trials comparing a single immediate intravesical instillation after TURBT, with TURBT in patients with single or multiple primary or recurrent pathologically staged Ta or T1 urothelial bladder cancers. The meta-analysis showed a statistically significant time to recurrence favoring the use of intravesical chemotherapy.

At five years, 44.8 percent of patients who received intravesical chemotherapy, and 58.8 percent of patients who received no treatment or placebo developed a new bladder cancer. For the three agents which had a positive effect on time to recurrence over placebo, the percent difference in effect ranged from an approximately 15 to 18 percent difference in time to recurrence.

Shown here is the basic study design for both SPI-611 and 612, which the applicant has already described. The primary analysis population is shown. This population was chosen because these patients were unlikely to receive additional therapy after the initial instillation of

apaziquone or placebo. This would, therefore, isolate the effect of apaziquone.

However, the results of central pathology review were not available to the sites at the time of TURBT, and the use of additional intravesical therapy was at the discretion of the investigator and was based upon local pathology review.

Finally, I will note that the applicant initially proposed the primary endpoint of time to recurrence, but after a consultation with the FDA, it was subsequently changed to recurrence at two years. This decision was based on the extensive use of endpoints such as 18-month recurrence and 2-year recurrence in the urology literature, as well as the use of endpoints such as 3 and 5-year disease-free survival in adjuvant trials.

This is to highlight the study endpoints for both studies. The primary endpoint again was 2-year recurrence rate, and secondary endpoints were time to recurrence, which included any new bladder cancer regardless of stage; time to progression to a higher stage or grade tumor, with

the order of progression shown beneath; and finally progression rate at two years.

We note that study 611 was conducted under a special protocol assessment, or SPA agreement. We point out that the study was designed to detect a 12 percent decrease in 2-year recurrence for patients treated with apaziquone compared with placebo.

This highlights the regulatory history of this application. As I mentioned, in 2007, an SPA agreement was given by the division for study SPI-611. Study 612 was designed to be almost identical.

In December of 2012, a pre-NDA meeting occurred where the topline results of both studies, 611 and 612, were presented by the applicant. Each study individually failed to meet the stated objective, namely an improvement in the primary endpoint of recurrence in the first two years. At the meeting, the applicant presented a pooled analysis of the primary endpoint from the two trials.

FDA informed the applicant that the pooling of data from two trials that did not meet the prespecified criteria establishing the efficacy of apaziquone would not be acceptable to support a regulatory approval. FDA advised the applicant not to submit an NDA based on these data, and it was noted that if they did decide to file their NDA based on the data, then a public discussion at an ODAC would be required.

The sponsor subsequently submitted their NDA based on study 611 and 612, three years later, in December 2015.

I will now discuss the FDA analysis of the efficacy for study 611 and 612. As noted previously, patients with clinically apparent Ta grade 1 to 2 disease were eligible for study entry. Shown here is a breakdown of the baseline central pathology for the ITT populations in both study 611 and 612. Highlighted in blue is the breakdown by arm for the Ta grade 1 to 2 target population, which made up the majority of patients, and which were the patients included in the primary analysis

population.

I will point out that between the two studies, 78 patients who had no evidence of tumor after a central pathology review received apaziquone.

The baseline demographics of patients on both studies were well balanced between arms and were similar when comparing the target Ta grade 1 to 2 population with all randomized patients. I note that study 611 was conducted mostly in the U.S., whereas study 612 was conducted mostly outside of the U.S. For the rest of my talk, I will refer to the Ta grade 1 to 2 as the primary analysis population.

Baseline demographics for the primary analysis population in both studies are shown here -- excuse me, disease characteristics. A substantial number of patients did not have low-risk disease, as evidenced by the presence of multiple lesions, lesions greater than or equal to 3 centimeters, or a prior history of non-muscle invasive bladder cancer. And this may imply that

this was not actually a low-risk group in the selected target or primary analysis population.

We performed an analysis to assess overall compliance with the scheduled cystoscopies throughout the course of the study, and we want to point out that there was a fair amount of missing data on these cystoscopies at each time point.

In our analysis, we looked at the number of patients who underwent their scheduled cystoscopies at each time point, and also accounted for patients who had not yet recurred at that time point. Given that the primary endpoint was recurrence at year 2, we will note that at month 24, among patients who had not yet had a documented recurrence, approximately 20 percent of patients on the apaziquone arm in both studies missed their scheduled assessment at month 24.

This is compared to 24 percent of placebo patients on study 611, and 8 percent of placebo patients on study 612 who also missed this time point assessment. When considering this, we note that the amount of missing data was greater than

the 6 percent difference in 2-year recurrence rate between the study arms on both studies.

Dr. Bloomquist will now present the FDA's statistical analysis of the two studies.

FDA Presentation - Erik Bloomquist

DR. BLOOMQUIST: Good morning. I am Dr. Erik Bloomquist, the primary statistical reviewer for this application. I'm here this morning to present the primary efficacy results and their associated statistical analysis.

To begin, the applicant relied upon four analyses to demonstrate sufficient evidence of an effect. However, after reviewing the application, FDA believes none of these analyses do demonstrate significant effect of apaziquone over placebo for the following reasons.

First and foremost, the primary endpoint in both studies 611 and 612 was not met. Second, the studies submitted with the application were not designed to test the time to event endpoint, and there's an uncontrolled false positive rate for the secondary endpoints.

Third, a pooled analysis by the applicant was done post hoc, precluding any interpretation of the significance levels and coverage probabilities. And fourth, a post hoc subgroup analysis is hypothesis-generating, but at this point does not provide convincing evidence for efficacy.

This slide presents the results of the FDA analysis of the primary endpoint. The numbers here differ slightly from the applicant's analysis in study 612. For FDA's analysis of study 612, we included three additional recurrences that occurred at the scheduled 24-month visit, even though the 24-month visit occurred after two years calendar time. Note that the inclusion of these three additional recurrences in study 612 only has a negligible difference from the sponsor's analysis of study 612.

As to the results, we can see that study 611 had an estimated odds ratio of 0.76 with a p-value of 0.11. In study 612, the estimated odds ratio was 0.78 with a p-value of 0.13.

Neither study reached statistical

significance at the 5 percent level. Because of this, neither study demonstrated statistically that apaziquone has an effect on tumor recurrence when compared to placebo.

To give some context for the estimated absolute difference in 2-year recurrence, please consider the figure at the bottom of the slide. As shown in the figure, in study 611, there was an estimated 6.6 percent difference between apaziquone and placebo in 2-year recurrence with a 95 percent confidence interval of negative 1.8 percent to 15.1 percent. In study 612, there was a 6.2 percent difference in the 2-year recurrence rate, with a 95 percent confidence interval of negative 2.2 percent to 14.6 percent.

Now, this point is very important. Since both confidence intervals contain zero percent, essentially no difference between apaziquone and placebo, neither study has demonstrated that apaziquone is different from placebo with respect to 2-year recurrence rate.

Some additional notes. Note that the

observed 6 percent is approximately half the expected difference of 12 percent that the studies were powered to detect. Also note, in the recent literature as presented by Dr. Lerner earlier, there's been a report of a 14 percent difference between instillation of other treatments and no instillation. However, study 611 and 612 only observe a 6 percent difference.

For the type of recurrences, most recurrences in the studies were low-grade Ta G1-G2, approximately 90 to 95 percent in both arms in both studies. Note that in study two patients on the apaziquone arm had their first recurrences as T2 tumors.

Based upon the analyses shown, FDA believes that both study 611 and 612 have failed to demonstrate sufficient or significant evidence that apaziquone has an effect on tumor recurrence when compared to placebo. Most importantly, the confidence intervals for the difference in 2-year recurrence in both studies contained zero, no difference, so neither study demonstrates that

apaziquone is different from placebo.

In addition, the estimated 6 percent difference was half the expected difference at the design stage that was considered clinically meaningful, and the 6 percent difference is less than half the effect reported in a recent meta-analysis comparing instillation of other treatments versus no instillation, as discussed earlier by Dr. Lerner.

Finally, as discussed by Gwynn Ison, missed cystoscopies the final visit could possibly diminish the observed difference in 2-year recurrence. Imputing the recurrence values for those without their 24-month visit, in a worst case scenario for apaziquone, could possibly give a negative 2 percent difference in the 2-year recurrence. Imputing the last observation as recurrence in both treatment arms, the 2-year recurrence could vary from 4 percent in study 611 to 7 percent in study 612.

Moving beyond the primary results, here are the results for the applicant's secondary analysis

of time to recurrence. In study 611, the estimated hazard ratio was 0.77. In study 612, the estimated hazard ratio was 0.81.

Although study 611 observed a p-value below the 5 percent level, we must interpret this station with caution. First, the applicant used a hierarchal testing procedure to ensure adequate false positive rate control.

Under this procedure, statistical significance for the secondary endpoints can only be declared if the primary analysis has been met. Thus, if we ignore this method of false positive error control, and erroneously declare statistical significance for the secondary endpoint of time to recurrence in study 611, we will have inflated the false positive rate beyond the prespecified 5 percent level.

In addition to these type 1 error concerns, however, we should still interpret the secondary analysis with care. This study was primarily designed to test 2-year recurrence rate, not a time-to-event endpoint. As such, patient follow-up

was truncated at the 24-month visit. If the study had been designed for a time-to-event endpoints, patients would have been followed possibility beyond two years until a prespecified number of recurrences had occurred.

Because of the concerns mentioned above, FDA does not believe the analysis of time to recurrence provide acceptable evidence of a significant effect.

In addition to the primary endpoint of 2-year recurrence and time to recurrence, the applicant has proposed two additional analyses to help support their application. The first is a pooled analysis of study 611 and 612, and the second is an exploratory subgroup analysis based upon the time from surgery to instillation of apaziquone. FDA however once again does not believe either of these analyses provides sufficient evidence of efficacy of apaziquone for the following reasons.

The first analysis relied upon the applicant is a pooled analysis of study 611 and 612, which

has the primary purpose to narrow the confidence intervals and to obtain a more precise estimate. But pooling the results of the two studies has little effect on the estimates of 2-year recurrence. The figure shown on this slide demonstrates this.

In the upper one third of the figure, we can see the estimates of 2-year recurrence and the associated confidence intervals for the two treatment arms in study 611. The middle one third of the figure shows the same estimates and confidence intervals in study 612. And finally, in the lower one third of the figure, we can see estimates of 2-year recurrence and the associated confidence intervals when we pool studies 611 and 612.

In the pooled case, the estimates of 2-year recurrence average the two study results, and the length of the two associated confidence intervals shrink owing to an increased sample size. However, the difference in 2-year recurrence remains essentially the same as study 611 and 612, 6 and a

half percent. Once again, please note that a 12 percent difference was considered clinically meaningful at the design stage.

Because the pooled analysis presented by the applicant has little effect on the difference in 2-year recurrence, and simply shrinks the confidence intervals as a function of the increased sample size, and this is an unplanned, post hoc analysis, FDA does not consider the pooled analysis as providing additional evidence beyond that provided by study 611 or 612.

In terms of regulatory guidance for the applicant's pooling analysis, FDA refers to ICH document E9, titled Statistical Principles for Clinical Trials. ICH E9 is an internationally recognized guidance document for statistical practice in clinical trials.

Per the document, individual clinical trials should always be large enough to satisfy their own objectives. And second, under exceptional circumstances, a meta-analytic approach may also be the most appropriate way, or the only way of

providing sufficient overall efficacy via an overall hypothesis test. When used for this purpose, the meta-analysis should have its own prospectively written protocol.

In addition to the pooled analysis presented, the applicant also focused on a subgroup analysis of time from surgery to instillation of apaziquone. The applicant believes that time to instillation is an important efficacy subgroup. The applicant hypothesizes that blood inactivates the active part of apaziquone, so instillation of apaziquone immediately after surgery decreases efficacy. The applicant has focused on individuals instilled 30 minutes post-surgery when bleeding would be possibly less of a factor.

As an aside, the applicant has an ongoing trial to test the efficacy of apaziquone in recurrent bladder cancer using an instillation window of 31 to 90 minutes.

For the results of the subgroup analysis, we can see in the table that the post-30 minute subgroup has an 11.5 percent difference at 2-year

rate of recurrence. FDA however is concerned whether the 11.5 percent difference observed could be replicated in a new trial. For the subgroup analysis shown, the 30-minute cut-off was selected after the results in both trials were known, suggesting that the 11.5 percent difference may be overly optimistic.

To assess this, FDA went back and reanalyzed the data using all cut points from zero minutes to 120 minutes at 5-minute increments. Using this strategy, FDA found that the 30-minute cut point provides the largest difference in 2-year recurrence for the greater than 30-minute subgroup.

Because the subgroup analysis used pooled data from both trials, after the outcomes were known, and are likely to be overly optimistic, FDA does not believe this analysis provides sufficient evidence of a claim of efficacy of apaziquone. Instead, this analysis suggests an intriguing hypothesis to test in the ongoing trial.

There is strong regulatory guidance to support FDA's position that the applicant's

subgroup analysis can only be considered exploratory.

First, turning back to ICH E9. In most cases, however, subgroup or interaction analyses are exploratory and should be clearly identified as such. When exploratory, these analyses should be interpreted cautiously. Any conclusion of treatment efficacy or safety based solely on exploratory subgroups is unlikely to be accepted.

Using another ICH guidance on clinical study reports, subgroup analyses are not intended to salvage an otherwise non-supportive study, but may suggest hypotheses worth examining in other studies or be helpful when we're finding labeling information, patient selection, dose selection, et cetera.

In conclusion, the applicant submitted studies 611 and 612 to demonstrate efficacy of apaziquone on recurrence in bladder cancer. After reviewing the application and data, FDA believes however that neither study demonstrate that apaziquone has an effect over placebo.

First and foremost, both study 611 and 612 fail to meet their primary endpoint, and the observed 6 percent absolute difference is less than a 12 percent different that was considered clinically meaningful at the design stage. In addition, the 6 percent absolute difference is difficult to interpret in light of the missed visits.

Second, the secondary analyses have an unknown level of type 1 error, precluding interpretation of the nominal p-values. In other words, we cannot rule out that the observed results for the secondary endpoint analysis and any subsequent analyses are not false positives here, and there is no assurance the observed effect is true.

In addition, the post hoc nature of the pooling analysis makes their associated significance levels uninterpretable, and really the analysis does not add any additional information beyond that provided by study 611 or 612. Finally, the post hoc subgroup analyses generate an

important hypothesis, but at this point do not provide sufficient evidence for efficacy.

In summary, the analysis and results have not demonstrated a significant effect of apaziquone over placebo. I'd like to thank the committee, and I'll turn it back to Gwynn Ison for the safety discussion.

FDA Presentation - Gwynn Ison

DR. ISON: Shown here is the safety overview for all treated patients on study 611 and 612. The applicant has already discussed the safety profile of apaziquone, and we do not have any major disagreements on the safety findings. We note that patients receiving apaziquone had an overall similar adverse event profile to patients who received placebo.

The table shown provides the incidence of grade 1 through 4 adverse events with the apaziquone or placebo during the first 7 days on study. This time interval was used to help isolate the effect of apaziquone. Note, however, that patients in both arms had recently undergone

instrumentation and tumor resection.

In summary, the FDA will first acknowledge that non-muscle invasive bladder cancer is an area of unmet medical need and is without question a difficult area in which to develop new therapeutic agents. Even if we consider this, with the current application, we have two trials, which fail to meet the primary endpoint establishing the efficacy of apaziquone.

Because of this, the FDA does not believe that substantial evidence of a treatment effect has been demonstrated. The difference in recurrence at two years compared to placebo was similar between trials with a point estimate of 6.5 percent.

We note that the confidence intervals cross zero, meaning that we cannot rule out the possibility that the effect of apaziquone is less than that of placebo. In light of the 20 percent missing data, this 6.5 percent difference is smaller than was expected, and its clinical meaning is uncertain. Post hoc pooling of the two studies to achieve statistical significance and the

subgroup analyses are insufficient to establish efficacy.

The applicant has conducted two trials of a single instillation of apaziquone versus placebo following resection of non-muscle invasive bladder cancers. The efficacy results are again shown in this slide. The safety profile was similar.

After discussion, we will ask the committee to vote, has substantial evidence of a treatment effect of placebo -- excuse me, for apaziquone over placebo been demonstrated? We will then ask this committee to discuss the following.

For those who vote yes to question 1, that an effect has been demonstrated, we would like you to please discuss the clinical meaning of the results of study 611 and 612. Thank you.

Clarifying Questions to the Presenters

DR. ROTH: Thank you. We'll move now to the question period from the committee to the presenters. So if you would please direct your questions to a specific presenter, if that's possible; and if not, then generally to the sponsor

or the agency and they can direct the appropriate person to answer that question.

If you would raise your hand, Dr. Tesh will take down your name in order, and I'll try to call on you in order.

So, if we want to start, Dr. Rini?

DR. RINI: So a question I guess for the sponsor in general, referring to Dr. Bloomquist's presentation, slide number 16, talking about the missing data. I wonder if the sponsor could comment on the amount of missing data. And he alluded to this, but if you yourself performed any sensitivity analyses around these data.

DR. BHAT: Sure. Thanks for the question. So as the agency explained, there were missing cystoscopies in these studies. Now, these are every 3-months cystoscopy for 2 years. In a typical AUA guideline or any guideline, 3-month cystoscopy is for the first year if there is no recurrence. But in the study, we mandated every 3 months, cystoscopy.

The missing cystoscopy may be for many

reasons. Slide up.

Let me just go through the numbers here. These are similar to what the agency has mentioned. So out of 295 patients in 611 -- let me just take the apaziquone arm in 611. Out of 295, 82 percent had complete cystoscopy at month 24. So the remaining 52, 17.6, had missed cystoscopy at month 24.

This could be for many reasons. One is, if they missed cystoscopy after recurrence, then it doesn't impact the primary endpoint because we already have the recurrence. Keep in mind, all patients are followed for 2 years regardless of their recurrence.

So the thing that may have an impact is a death, which is discontinued from the study, AE,] discontinued from the study or lost to follow-up for a variety of reasons.

If you look at the last three rows, especially the bigger one, due to other reasons, the two groups are essentially the same. And this is a double blind study, randomized study, where we

don't know -- our patients don't know what they get.

This is the distribution of the missing data. Although it is up to 20 percent, the real missing that impacts the primary analysis is for 10 percent or less.

DR. ROTH: Ms. Speers?

MS. SPEERS: My question I guess is for the sponsor. The toxicity profile looks really good for this drug, especially compared to mitomycin C. Did you have any patients that did have perforations, and what those side effects might have been with this drug?

DR. BHAT: We did have some perforations, but those are all unrelated in our treatment, and they are equally distributed between apaziquone and placebo. In 611, both studies together, there were 4 in apaziquone and 4 in placebo. And they were all grade 2, grade 1, and none of them are related to our drug.

DR. ROTH: Dr. Logan?

DR. LOGAN: I had two questions. First is

related to slide CE-18 for the sponsor. I just wanted a confirmation from the sponsor that the subgroup -- this is a subgroup analysis. I just wanted confirmation from the sponsor that the subgroup analysis was added after the data was available to the SAP.

DR. BHAT: Yes. Our primary endpoint is the overall analysis Ta G1-G2. This subgroup analysis was done, the post hoc as agency said, and as we said. It was not prespecified. But the important thing here is, there is a pharmacology reason that we explained, which is drug inactivation on mechanism.

That's why we're looking at, the pharmacology drug inactivation, is it providing some signal or no signal in our studies. And as you see, in both studies, those two large studies done in different countries and different hospitals, with the different TURBT procedure, we have seen similar improvement, which is much higher in patients instilled more than 30 minutes.

DR. LOGAN: Yes, but of course the agency's

concern that you're optimizing the cut point to show the biggest treatment benefit is a major one, and it's the reason it really shouldn't be considered anything but hypothesis-generating.

My second question was about the primary endpoint itself in slide CE-8. So if I'm reading this correctly, you're doing this as a simple proportion of patients with a documented recurrence. So the patients that have incomplete follow-up are treated as no recurrence?

DR. BHAT: Yes. Along the line of the sensitivity analysis, or the missing cystoscopy, we have done several sensitivity analyses. So, as I mentioned, about 10 percent in both arms in 611, and less than 10 percent in 612. Slide up.

We have done the sensitivity analysis multiple different ways. Let me orient the slide first because there are a lot of numbers here.

For each study, 611 and 612, the first row is the original analysis, 6.7 percent and 6.6 percent differences. The sensitivity analysis, one, is to treat all patients who were lost to

follow-up prior to month 24 as a failure, or as recurrent, it recurred, because we haven't seen the recurrence but they were lost to follow.

When you look at the sensitivity analysis of one, we still have similar improvement, 7.5 percent, in fact it is higher, and 5.1 percent in 612. So we also did the other sensitivity analysis, which is more of a completer analysis. It's a sensitivity analysis, too by excluding all the patients who did not recur or missed lost to follow-up, or missed last visit.

So numbers are lower, 257 in 611 for apaziquone, and 256 in 612 for apaziquone. I'm just using one column to illustrate my case. So when you look at that, the treatment effect is in fact much higher. It is a little higher than the overall in the completer analysis.

DR. LOGAN: Okay. But these sensitivity analyses don't address the FDA's concern that if there's differential recurrence rates among that missing data in the two arms, that may shrink the treatment effect.

DR. ROTH: Dr. Uldrick?

DR. ULDRICK: I had also a question for Dr. Bhat regarding the methodology for the pooled analyses. It seems that the studies were almost identical in terms of patients, intervention, and evaluations. I was wondering if there were any formal evaluations of heterogeneity between the two studies, is the first question.

DR. BHAT: When we looked at all the baseline subgroups -- let me start with the patient disposition, or patient characteristics. As we've shown in the presentation, the baseline subgroups, they're all pretty similar between studies. And when we did the analysis as part of the pooled -- slide up -- let me go through the baseline distribution.

As you see, the age is the same, mean or median age. The proportion of elderly population is the same. And the race and gender, they are similar between two studies.

DR. ULDRICK: And the second follow-up question is related to your sensitivity analyses.

You've presented the sensitivity analyses for the missing data on the individual studies, but I do not believe I've seen it for the pooled studies. And additionally in the briefing document, you showed intention to treat for the entire cohort for the individual studies but not the pooled studies. I was wondering if you had any sensitivity analyses on the pooled data.

DR. BHAT: We haven't done the sensitivity analysis for the pooled data, but as you said, we have done the ITT analysis for each individual studies. And the effect, treatment effect is positive, although that includes non-target population.

Keep in mind our target population is Ta G1-G2. So the non-target -- slide up -- population includes some of the T1, you know T2 or Ta T3. If you look at the differences, they are positive, and they are slightly lower than the target population, but they are reproducible in two studies.

DR. ROTH: Dr. Kim?

DR. KIM: We would just like to clarify the difference in the numbers that were presented for missing bladder assessments. Could we have FDA's slide 16 and Dr. Ison will clarify.

DR. ISON: So once it comes up. We just want to clarify that the analysis we did, did take into account the patients. We took the patients who had already recurred out of the denominator. So these were truly patients who had not yet recurred by the month 24 visit, and these were the missing assessments, so the number of patients who had missed their assessment and had not yet recurred ,so.

DR. ROTH: You didn't have another question, did you?

(No response.)

DR. ROTH: Dr. Nowakowski?

DR. NOWAKOWSKI: Question to the sponsor. It has been implied by the sponsor medical experts that the major benefit to the patient of reduction in recurrence rate would be the reduction of transurethral resection, or need for transurethral

resection.

Was it included as a study endpoint, and do we have any data to support it from the study?

DR. BHAT: Can you clarify the question?

DR. NOWAKOWSKI: It has been implied that reduction in the tumor recurrence rate will result in a decreased need for transurethral resection of the tumor; hence, it will benefit the patients because there's no impact on overall survival, there's no impact on development of muscle invasive disease.

So the potential benefit to the patient of this therapy would be that less transurethral resection would be needed. As such, less invasive procedure, potentially less complications of those.

Do we have any of this data in the study? So did we show that actually less transurethral resections were performed?

DR. BHAT: In the study, this is a 2-year study. And when a patient has recurrence in 2 years, they may have undergone TURBT. But we haven't collected need for TURBT as an endpoint or

data collection in this study. But let me have Dr. Neal Shore comment on this, please.

DR. SHORE: So, thank you. I appreciate the intent of that question; it makes perfect sense. So I can tell you that in the United States, the overwhelming majority of urologists will not sit on a patient who can meet some level of a performance status for anesthesia and just watch their tumors without resecting at a certain point in time. So by definition, recurrence of tumor will obligate a physician, urologist to resect that tumor.

DR. NOWAKOWSKI: I would assume, however, that some of those resections would be tumors who could be pathological response, but there are still some lesions seen in the bladder, or would it be unlikely?

DR. SHORE: I'm sorry. I didn't really follow you. Say that again, please.

DR. NOWAKOWSKI: Are there any situations in which you would perform resection of the bladder lesions, which would not be a pathologically confirmed tumor during the follow-up cystoscopies?

DR. SHORE: There's always a potential that the urologist can be fooled and think that they're resecting some sort of inflammatory lesion, or what appears to be a malignant tumor. But I think, as Dr. Lerner said in his presentation, as well as Dr. Soloway, overall well-trained urologists do, and 95 percent of the time are highly accurate in predicting the pathology. But to your point, that's why we have pathological review.

DR. NOWAKOWSKI: Thank you.

DR. ROTH: Maybe I could squeeze in something here. To follow up on Dr. Shore's point, and Dr. Soloway's comment before, that people are 90 percent effective, well in this study, it was only 70 percent correlation from a pathologic standpoint.

So as we think about this being used widespread, then that might have some impact, and it may not be the top bladder cancer experts at academic medical centers that see hundreds of cases a year. It may be the person like some of these places that put on one patient a year, so I think

that has some implications.

I had just a couple questions. Since one of your endpoints is time to recurrence, how did you deal with the positive cytologies? So let's say the patient at 3 months has positive cytology, negative cysto; at 6 months positive cytology, negative cysto; at 9 months has a visible lesion. What's the time to recurrence?

DR. BHAT: In our studies, the recurrence determination is primarily -- it's only based on the central pathology of review of tumor specimens. We haven't taken a look at urine cytology as part of the determination of the recurrence.

DR. ROTH: Okay. Ms. Speers?

MS. SPEERS: My question has to do with the choice of the 12 percent reduction in recurrence at 2 years. And it seems like the mitomycin C in some of the other data was all based on a reduction of recurrence after 5 years. And so I'm not sure how that was chosen or what the comparator is, and how the 6 percent kind of plays in that.

I'm trying to grapple with what is the

clinical meaningfulness of that 6 percent at 2 years versus 14 percent at 5 years, and where the 12 percent actually came from.

DR. BHAT: I will have Dr. Fred Witjes comment upon it. But just to give you an idea, that was based on meta-analysis of last 30 years. Over this time, the technology has been improving. So therefore, I would have Dr. Fred comment on this, please.

DR. WITJES: I would think you already gave the answer. Yes, we realize that the meta-analysis Richard Sylvester did in 2004 is based on some [indiscernible] studies from the '80s and the '90s. And even the reanalysis he did in 2016 is based on the same studies. He's retired, so he has a lot of time to reanalyze a lot of studies.

But those are all studies from an earlier era where we didn't have digital cystoscopy, where we didn't have good video control. So I don't think -- I've been part of those studies. I think we do a better resection nowadays.

You also have to realize that those studies

were almost all against no other treatment, so not placebo but no other treatment, a TUR only. That is a little bit different. Maybe the difference is a few percent, but there is a difference between only bladder instillation with water or whatever and no treatment at all.

So I think you're a little bit comparing apples with oranges if you would compare the 12 percent of 2004, which we then thought was relevant, and the 6 percent that we have found, or the 6 percent that we now consider relevant.

DR. ROTH: Dr. Gonzalgo?

DR. GONZALGO: It's good timing. I had questions related and follow-up to previous questions. Just to clarify again, I think Dr. Shore had commented -- again, there may not be the granularity to look at the specific characteristics of the tumor recurrence, but the argument is being made to reduce trips to the operating room.

If there's any indication of how the tumors in either cohort recurred, whether they were

solitary, multi-focal, whether or not these could have been handled by office fulguration, because we know many -- given the fact that these patients will have already had an existing diagnosis on initial TUR of low-grade disease, so they fit in that category where if a patient were to have recurred with a solitary tumor that was 2 millimeters in size, we could see an office urologist simply fulgurating that rather than taking them to the OR.

So again, I'm not sure if you have the granularity to do that. That might be helpful to help us understand the argument for a reduction in trips to the OR.

DR. ROTH: Dr. Shore?

DR. SHORE: I think that's obviously a very good point. We have a lot of variability how we in the community, as well as in academic centers, would treat various sized tumors, how we're set up in the office versus ambulatory centers and patient schedules.

So there's no doubt that recurrent disease

can be handled in different ways, but for significant numbers of patients, they'll end up having a requirement for either an anesthetic cystoscopy, biopsy, fulguration, or some form a full on TURBT.

I just want to make one other comment back to Dr. Roth. These low-grade tumors invariably never have a positive cytology. It's only in our high-grade lesions that we find positive cytology. There's a real unmet need for low-grade tumors to come up with biomarkers, so that's one of the reasons why that was not of great significance in this particular study. Cytology is particularly good for high-grade lesions and carcinoma in situ.

DR. ROTH: Well, that brings up a point. I was thinking more about the people who were misdiagnosed as low grade. So 30 percent of people had something else, had either CIS, had some T1, T3, a couple muscle invasives. And the treating physician blinded the results of central path review, correct?

DR. SHORE: Correct.

DR. ROTH: So I guess I'm trying to wonder what the impact of a single dose of apaziquone, or placebo frankly, for suspected low-grade disease, and that patient's actually being undertreated because they would have been treated differently for T1 G3, for example, and what impact that has on the recurrence pattern.

DR. SHORE: Well, I think that concern is across the board on any IPOC trial that would be done. There's always going to be a very small subset of patients who are misinterpreted cystoscopically.

DR. BHAT: If I may ask Dr. Soloway also to respond to the question that was asked before.

Dr. Soloway?

DR. SOLOWAY: I must say, I'm very impressed with these comments. They're really superb questions. One point, maybe to elaborate on Dr. Gonzalgo's excellent point, my perception, and I've been interested in endoscopic resection of bladder tumors for many, many years, is that, first of all, outside of the United States, almost every

patient with a bladder tumor goes to an operating room suite, Australia, England, often in Canada. It's amazing.

Here we take for granted that we do a lot of office endoscopy. Around the world, most urologists do not have flexible endoscopy in an office setting. That's a huge expense to the total general care of bladder cancer, and I think that's important, very under-evaluated.

Office fulguration would be greatly benefited by an easy, safe intravesicular therapy. I didn't bring it up in my talk because of time. Office fulguration is very infrequently utilized in the United States. That's where education would be tremendous. Patients are going to the operating room for absolutely no reason in a large percentage of these patients, for reasons I don't understand.

So a very effective therapy for these small -- that's why I emphasize subsequent tumors, as we all know as urologists, tend to be very small because the patients are under surveillance every three months. They're easily be applicable to a

very simple office procedure, which is, again, as I mentioned, not very often performed, and then follow that by intravesicular therapy.

The big question here, or the big elephant in the room as I see it -- and I understand all of the scenarios, is 6 versus 10 or 12 percent. That is a moving target. The point is, if we benefit 6 percent of patients in this category, it's a major benefit to the patient.

If it was my family member, and you say, you could get a very safe application, which is highly likely to provide some benefit to you right here in the office and prevent you from all the problems, and expense, and time off, et cetera, of your family, because these are often elderly people going to the operating room, I think 100 percent of patients will say, sure. If it's very safe, give it to me, if it's a 2 percent or 4 percent benefit.

DR. ROTH: Dr. Chamie?

DR. CHAMIE: I'd like to make one comment, and I'd actually like to ask either the agency or the sponsor to comment on this. The first comment

is, I think the notion that urologists can identify the grade or stage of the tumor of 95 percent is not accurate. We've looked at this at population level, and it's probably about 50 percent. Actually, in this study, it was about 25 to 30 percent, that they were mistaken. So 70 percent accuracy in a clinical trial setting, in a population level, it's more about 50 percent.

The one question, either for the agency or the sponsor, I think when you're looking at mitomycin C's effectiveness, and you're holding any new potential drug in this platform up to that 12 or 14 percent is a little bit of a high bar to reach. And I think part of that is because I think most of it was done in patients who received TURBT alone.

There's been two studies, both from Japan, that have actually looked at continuous bladder irrigation for 24 hours that have been shown to be just as effective as mitomycin C. At our center, we've looked at just one hour of bladder irrigation, and that that was associated with no

significant difference between mitomycin C.

So if we're going to make the argument that any new potential drug has to meet mitomycin C, at least we have to hold it to the same standard, and that is do we know what is the efficacy of mitomycin C compared to saline irrigation.

DR. KIM: We'd like to respond. I think that's a great point, and I think the point that we don't want to go to is to do cross-trial comparisons between apaziquone and mitomycin C. I think in considering the 12 percent effect size that was hypothesized, sometimes the reason why we look for large magnitudes in treatment effect is to be certain about the possibility that there is a treatment effect.

There are two ways that we could do that. One is to have a smaller trial with a larger effect in study, or to increase the sample size of the population to go after. Either way, what we're looking for is a prospectively designed trial to answer those types of questions.

But certainly the discussion -- and most of

us, the review team, were not here at the time of the discussion between the sponsor -- or the applicant and the FDA in designing the trial metrics. That was for the purposes of a special protocol assessment agreement, to say that this is the sample size that is reasonable, and the trial design elements that are reasonable. That's an agreement.

Most of our approvals actually don't occur under the special protocol assessment agreement. That's not a requirement for approval, so applicants are free to design the trial as they see fit.

So I'm not sure that -- I think it's what's been communicated, seems like that was an FDA requirement to set the bar for 12 percent, and that's actually not true. That's an agreed upon sample size and design element. However, the sponsor and applicants in general are free to design trials as they see fit to communicate the clinical benefit of their drug in the intended population.

I think what we're here seeing now is the results of things that didn't go quite as well as expected, and here that's the discussion that we're having.

DR. PAZDUR: But to answer your specific question, which points to is there a comparative efficacy standard, and the answer to that is no. You do not have to show that this is better than mitomycin. You have to have substantial evidence that you believe that there is an effect here, okay.

That's the primary question. It's not are you better than mitomycin. And then that effect, if you believe that it does occur, has to be put in the context of a risk-benefit analysis.

DR. ROTH: Dr. Cole?

DR. COLE: One quick comment. I just want to note that when we talk about the 6.7 percent benefit and what that translates to, we should keep in mind that that estimate has errors associated with it. And that error, even in the pooled analysis, doesn't include effects as low as

1 percent benefit. So when looking at those numbers, one does have to appreciate that.

I'd like to follow up as well with a question for the sponsor. Dr. Bloomquist I think made the point that post hoc and pooled analyses will have higher false positive error rates. In fact, we know that they can be much higher. This is very well known.

However, based on the conclusions the sponsors made, you seem to disagree. You seem to disagree that inflated false positive error rates is a problem. And I would like to know really clearly why it's not a problem.

DR. BHAT: Let me start with the prespecified analysis. As you saw, we acknowledge that we haven't met the prespecified analysis. That's purely based on the powering. As you also heard, that our powering, from FDA as well as us, the powering was based on 12 percent. That 12 percent was originally taken from Sylvester's 2004 meta-analysis.

As Dr. Witjes said, the studies were done in

the '80s and '90s. And since then, there's a lot of movement or evolution in terms of the treatment effect of TURBT alone.

So when we looked at the recent literature, obviously these are all post hoc. I acknowledge that ahead of time. And the studies showed 5 percent, studies showed 8 percent, and also, the recommendation is 6 percent.

In our study we do have a placebo. It's not TURB alone. So you had to take that into consideration as well. So in Sylvester's meta-analysis, whether it's 2004 or 2016, it's the same study. He just used individual patient data analysis to do the time to recurrence in 2016; 7 of the 13 studies are the same studies back in 2004.

When we looked at the studies -- slide up -- studies in a TURB-plus placebo -- and those are in the orange dots, and the blue dots are TURB alone -- you can see clearly there is a difference in terms of the treatment effect in those analyses, or those studies that he included. And if you look at the orange dot only, we can compare ourselves

pretty well.

I know I'm not answering your question yet, but the question is, we started with the wrong premise of detecting 12 percent in our studies, when in fact 12 percent is on shaky ground.

Come to the next point about false positive, inflating false positive. Our study used 2-year recurrence rate as the endpoint, as per FDA agreement. But I haven't seen any study in Sylvester's meta-analysis, it is based on time to recurrence. And I don't know where the literature is for a 2-year recurrence rate, because Sylvester's analysis, his two analyses have the biggest analyses in this disease space.

If we look at the time to recurrence, that's something we have to take into consideration, although it is secondary endpoint. When you don't meet primary endpoint, secondary is inflating false positive, but I do agree all those things.

But the other point we want to bring in here, which is a post hoc, we agree, is the drug inactivation part. We have 40 percent of the

patients instilled within 30 minutes where there is a lot of blood. So if you take that out, if you look at the time to recurrence, which is the relevant endpoint, we have met significance in both studies, post hoc, I agree. But that is something you need to take into consideration when you are looking at the substantial evidence of efficacy.

DR. ROTH: Dr. Bloomquist?

DR. BLOOMQUIST: Could we move to FDA backup slide number 47, please? This is to answer Ms. Speers' point regarding the 5-year recurrence. I know we've been talking about 5-year recurrence because that's really what Sylvester has done in his meta-analysis. But to get an idea for 2-year recurrence, what we can do is go back to the Kaplan-Meier plot and sort of interpolate on the Kaplan-Meier plot. And that's next slide, please.

This is what we've done here. This is the time to first recurrence based upon the Sylvester paper. And what we've done is just simply interpolate it as best we can, as fairly as we can, at 2 years, and then we draw two horizontal lines

at the two curves, and we detect approximately a 14 percent difference.

I mean depending on where you draw the lines, I guess it could be 12, 10, maybe 16, but as fair as we could, we thought even at 2-year recurrence based upon Sylvester, there was a 14 percent difference between instillation and no instillation here. So I just wanted to clarify that point for you.

DR. ROTH: Chairman's prerogative to not butcher your last name, so we'll call on Vali for the next question.

DR. PAPADIMITRAKOPOULOU: Thank you. Actually this is exactly the point that was just made. I wanted to ask the sponsor to reassess their position about the primary endpoint and the 12 percent difference. If they looked at this data today and we wanted to make the argument about clinically meaningful effect for these patients, what would be the rate that we would consider it clinically meaningful? Of course, it would have to be associated with statistical significance as well

for the 2-year recurrence rate.

DR. BHAT: That's a very good point. Before I call Dr. Soloway, I would like to clarify one thing, that in our studies, the placebo was a vehicle that we used in apaziquone. Apaziquone is especially made for intravesicular use. We have a special formulation. And in the study, we had a matching placebo. So propylene glycol, which is the vehicle of the apaziquone, was used as a placebo, number one.

Number two, we had color matched it. By using eggplant extract, we made a purple reddish color, and we used exactly 60 minutes. So the placebo was instilled just like drug, and within 60 minutes, patients were asked to void urine and collect the drug.

So I just want to make sure that placebo here is more than just TURBT, or just water, or just saline.

Dr. Soloway, may I request you, please?

DR. SOLOWAY: I sort of feel like you're asking me as King Solomon to come up here and tell

you what the magic number is. I mean, the people here on this panel in front of me deal with this much more.

As a urologist, on the one hand -- I mean, I'm going to go a little bit off here, but talk about neoadjuvant chemotherapy prior to muscle invasive bladder cancer. I remember very distinctly a very famous, quote/unquote, "famous" medical urologic oncologist, if you will, at Memorial saying it's malpractice for the 5 percent benefit not to offer a patient neoadjuvant chemotherapy.

I understand, there's a survival benefit there. We're not talking about survival benefit, but we're talking about a drug, combination of drugs with potential mortality. So again, that's 5 percent. You must do it, or you are absolutely wrong. And as you know, 50 percent of urologists don't follow that and don't do it.

You're asking me what's the number here. Again, it's a very safe drug. It's very underutilized. We keep bringing up mitomycin. In

fact, mitomycin is pretty infrequently utilized for all the reasons we've talked about, and BCG is not an alternative.

I just had a TURBT on a 94-year-old the other day. And I swear as I'm standing here today, the family asked me, look, my dad, we're very concerned. We love him very dearly. Isn't there anything we can reduce the chance he's going to have to come back to the OR.

He had already googled, and I said, yes, there's intravesicular therapy. So what I said is, I'm going to get him over the procedure, come to the office, and I've already started intravesicular therapy on this patient because they were relatively, quote/unquote, "superficial tumors."

I can't give you a magic number. Honestly, as I said before, it's true; 3, 4, 5, 6 percent, that's fine for a very safe drug to use in the office or in the OR, as can be easily performed, to me is a significant benefit, again because it's this population of patients that are often very elderly, and you really don't want to take them to

the OR. That's the best answer I can give.

DR. BHAT: I would also like to request Dr. Witjes to come and add.

DR. WITJES: Well, thank God I'm not a statistician. That's not a statement. But anyway, we do have to realize that it is a very effective drug. We worked with that in the '80s when it was discovered in Amsterdam by Eef Oostveen. We did some in vitro studies. It's a very effective drug.

So we took it to the EORTC. Some of you may know that. We used it in solid tumors; didn't do anything, nothing at all, because it is totally inactivated in blood in a few minutes.

You know, systematic admission without passing blood tests is of course very difficult. So we thought, well, let's do it in the bladder. I have done a marked lesion study, and it really is very effective. There, you don't have the blood problem.

We didn't realize when we started this study around 10 years ago that there might be influence of hematuria after a TUR with a small tube, but

apparently it is because if you do the sub-analysis -- and I realize it's post hoc. But if you do the sub-analysis and exclude the patients with hematuria, it really is much more effective than those 5 or 6 percent.

Maybe, Larry, you can comment on that because he is the largest enroller in the study, and he has the experience with no hematuria in these patients.

DR. KARSH: Good morning. My name is Larry Karsh. I'm an attending urologist at the Urology Center of Colorado. I am the director of research. We have 17 urologists, a radiation oncologist, and have incorporated a medical oncologist into our practice.

I have been practicing for over 30 years, and I have almost 20 years' experience in clinical trials. And I've been a principle investigator in over 200 trials.

In 611, I was actually the highest enroller, even in the international series. We had 62 patients enrolled, 45 were identified as the

target. Slide up.

I've heard Susan Holliday in the past say that tortured data will confess. We pulled out the data, tortured it, and here's my confession. This is, on the 45 patients, what we had was an 11 percent reduction in recurrence, with an odds ratio of 0.46 and a relative recurrence of 47 percent.

Now, when we look back, we just happened to have most of our patients, 98 percent of our patients had instillation after 30 minutes. Seventy-five percent had instillation within 30 to 90 minutes.

Now, I'm not a genius. I didn't know what we were getting into when we started the trial. It just happened that the way our system is, we bring the patient from the OR into the PACU. We have everything in one center. Our research people were ready there, instilled the study product, and that's how we got to that number.

I've found this drug to be very safe. We've also been involved in some other [indiscernible]

drugs, the new 305 trial. So it's very safe. It's tolerable. So why would we want to approve this drug now? The data is here today. The drug is efficacious. The drug didn't fail, the trial failed.

We have evidence from two of the largest, well done, randomized, placebo-controlled trials demonstrating safety and efficacy. And from a standpoint of a clinician treating bladder cancer, I want an FDA approved agent that is safe, efficacious, and has minimal toxicity for my patients in low to intermediate bladder cancer.

As urologists, we don't think like oncologists. We don't use off-label oncolytics. We tend to want to be on label. And when you hear some stories about what the potential side effect from one instillation of mitomycin could result in a cystectomy, we're petrified. We get pretty nervous about it. So you can see that there's probably a low adoption. That may be one of the reasons.

But I think if we had a label, on-label drug

that is formulated specifically for the bladder, that we would probably have a higher adoption among urologists. There'd be some education. Because I was a non-believer. You had that pie graph up there. I used to be a non-believer until I did this trial, and I do believe that there are some effectiveness to doing that. But I proceed with trepidation.

I'm concerned about some of the potential side effects that we get with these agents, and there has been no -- I've been practicing. All my career, there was only two drugs that have been approved during my career -- we talked about that -- the BCG and valrubicin, and they're for high-risk patients.

There's nothing on label for a low-risk patient. And I think in order to move this field forward, we have to have something to compare to, and something that people will use.

In bladder cancer, we're kind of 10 years behind prostate cancer. The prostate cancer working group 2 actually laid the foundation for

recommendations of rational trial designs that led to endpoints, rational endpoints. And then ever since 2010, we've got six new drugs that have been approved on different mechanisms of action and overall survival.

We've got to move bladder cancer forward, and we need to make some progress. It may be small steps at a time. But I think when you have a therapy like this, that's been shown to be safe, efficacious, and well tolerated, that we need to really consider giving that to us in the field. We need that in the armamentarium.

So I think that if we had this drug today, it would help avoid unnecessary TURBTs due to recurrences. And this is in predominately an elderly patient population, who commonly have comorbidities with more potential for post-operative complications. There's nothing less than I want to do than take a patient with complications to the OR.

To wait another four to five years for this agent to be approved, really equates, you know

whatever numbers. If we say it's 80,000 to 100,000 procedures that can be avoided, that would be a major benefit for our patients if we approved apaziquone today.

DR. ROTH: Thank you. Dr. Pazdur?

DR. PAZDUR: I had a question, but it's really for the panel, or for really the two statisticians on the panel, because I'd like them to discuss this.

In reference to the past gentleman's comments, we all wish for new drugs. If that was the reason why we were here, is just because we wanted to fulfill a wish for a new drug, we would not have convened this committee together.

I have also noticed people throw around the terms "efficacious," "statistical significance." And one of the reasons why we put the questions in this context, is there substantial evidence. And then if and only if you have demonstrated substantial evidence, is there a benefit to this drug.

We first have to know is there an effect

here. Is there an effect? It's not the wish of an effect, but what has been actually demonstrated. And a lot of times people take a look at a 0.05 value, and they say, oh, if it's less than 0.05 it's statistically significant. The answer to that is, no. Okay? It has to be put in the context of a statistical plan and a reference p-value to make a determination here.

So I guess what I would like to have our two statisticians here comment on is what has been shown from a statistical point of view? And I'm not talking about just being less than a 0.05 level.

DR. LOGAN: So I completely agree with your point in general. So before we start talking is 16 percent clinically important for the patients, we have to establish whether the data suggests that there is actually a robust evidence that there is a benefit. I don't think that we see that so far. If you look at the two primary trials, neither one of them met their target of establishing evidence at a 5 percent significance level.

The sponsor has discussed this pooled meta-analysis, which they say is statistically significant at a 5 percent level. A meta-analysis -- so even throwing aside the issue of not having a prespecified plan for the meta-analysis, which introduces additional uncertainty about how reliable those results are, but even throwing that aside, the level of statistical rigor that a single meta-analysis at a 5 percent level has versus two trials, both meeting a target of efficacy at a 5 percent significance level, those are two different thresholds.

If you consider the false positive rate associated with them, meeting a significance level of 5 percent on two randomized trials is associated with a false positive rate of about 5 percent squared, or 0.25 percent. If you look at the meta-analysis, that's got a false positive rate of 5 percent. So that's much more uncertainty in terms of whether there's a real benefit here if you look at the combined meta-analysis results.

So that's just one aspect. Then as I

mentioned, there is the uncertainty with the lack of a prespecified analysis plan for the meta-analysis.

The other issues that have been raised, the secondary analyses is a major issue. If you don't establish that the primary analysis is significant, you don't have any alpha or any significance level to even look at secondary analysis. Any looks at those is going to inflate the false positive rate and increase the chance that you're making a mistake, concluding that there's efficacy when there really isn't.

Then the subgroup analysis is a post hoc analysis. The estimates that have been shown for the subgroup of more than 30 minutes instillation period, those are likely to be biased because of the post hoc selection of the cut points.

So I guess my take is that there isn't -- that I totally agree that you have to establish that there's robust statistical evidence that there is even an effect here, and I don't think that bar has been met.

DR. ROTH: Let Dr. Gonzalgo make a quick comment, and then we'll come to Dr. Cole.

DR. GONZALGO: Could you please pull up the FDA's slide 20 in the FDA statistical analysis packet>? As a urologist, it would make me the happiest doctor in the world to be able to assure a patient that addition of this intravesicular agent would somehow be beneficial. At the same time, I don't want to provide any type of false hope or misleading the patient that this is going to give them the chance to remain disease free.

So as a follow-up to this specific question, I don't know either Erik or Brent, just comment on the top point and helping me understand the benefit. We've talked 12 percent, 6 percent, but this is the data. And I just want to know, in the context of telling the patient, how much better is this than doing nothing?

DR. LOGAN: So the important point to consider here is, in terms of level of statistical evidence, that there's a benefit here. The confidence interval shows you plausible values that

are consistent with the data. So the estimate of 6 percent, about 6 percent, but the confidence intervals include zero in those intervals, for both studies. So zero, zero benefit, no benefit at all to this treatment is consistent with the data, at this point.

DR. ROTH: Dr. Cole?

DR. COLE: I agree completely with Dr. Logan's comments. And just from a more simplistic kind of viewpoint, this is what I tell my students how not to do things. And that is, if you get a result, you do an analysis, you get a result and you don't like it, you add data, and you can keep doing that, and eventually you get the result that you want. And that's true.

We have to be really careful when we add data to a study, and then reanalyze and try to make a conclusion out of it.

To answer Dr. Pazdur's question, I don't know. I don't know the actual false positive rate of this kind of study design, where you run two separate studies, neither one reaches the primary

goal, and then you pool results, and get an answer. I don't know. And Dr. Bloomquist actually said that in his presentation very well; it's unknown.

DR. ROTH: Maybe just wrap this up. I had one brief question because I couldn't tease it out of the paperwork. In the ongoing phase 3 trial, what magnitude of benefit is that trial powered to detect?

DR. BHAT: The ongoing trial 305, the primary endpoint is time to recurrence. It's not a 2-year endpoint. And we have the SPA with the FDA. The FDA agreed to time to recurrence based on the lesson learned.

In terms of powering, the time to recurrence hazard ratio powering for 0.81.

DR. ROTH: Okay, thank you.

If there are no other questions, I think we'll take a 15-minute break before opening to the open public session, and so we'll reconvene at 11:05.

(Whereupon, at 10:50 a.m., a recess was taken.)

Open Public Hearing

DR. ROTH: Thank you. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that they may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this

issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 please step up to the podium and introduce yourself? Please state your name and any organization that you're representing for the record.

MR. KRIVEL: By way of disclosure, the

applicant paid for my travel and lodging, but I have no financial relationship at all with the applicant.

Good morning. Thank you for the opportunity to share my journey with bladder cancer with you today. My name is Mark Krivel. As I mentioned, I'm 57 years of age, and I was diagnosed with bladder cancer eight years ago. At that time, I was treated with a test medication, apaziquone, and I'm cancer-free today.

On July 21, 2008, I remember that date well because it was my wife's 50th birthday, I noticed there was blood in my urine, which has never happened to me before, so I was quite concerned. I was reluctant though to tell my wife about it because it was her birthday. I didn't want to worry her. We had a concert to go to, but it weighed on me.

So I did tell her, and she got obviously concerned, said this wasn't normal, which I knew, and told me I need to see a doctor immediately. And when she tells me something, I need to do that,

so I absolutely did.

I made an appointment with my general care practitioner for the next day actually, and he had me run -- he ran urine tests, had me go and they did some images. And he called me the next day and told me that it looked like I needed to make an appointment with the specialist and do so right away. And I was certainly concerned, but I did that. I did that right away. And he gave me the name of a urologist to make an appointment with.

I got in with that urologist right away, and exactly one week after the initial diagnosis, a tumor was removed from my bladder. I was also treated with the test drug, apaziquone, the subject to my comments today. It's been eight years since the post-surgical single treatment of apaziquone, and I remain cancer-free as I stand before you today.

I'm going to backtrack a moment, though, to my initial meeting with the urologist, Dr. Larry Karsh, eight years ago. My wife and I went to the urology appointment with Dr. Karsh, and

at that time, he identified a tumor in my bladder. Based upon the exam and cystoscopy, and the fact that the system of blood in my urine had just started, you know like I said, the day before, a couple of days before, his initial diagnosis was the tumor appeared to be isolated in the bladder.

He explained this would be the best case scenario if it had not gone beyond that, it had not spread from the bladder to other sites. But we would not know conclusively until he did the surgery, and we got the pathology report, and all that. So like I said, everything was pretty quick.

Dr. Karsh went on to explain the clinical trial that he was involved with of a medication that was being tested that helps to prevent bladder cancer from recurring once it has been surgically removed. He explained the medication is designed in patients that had the type of cancer that I was identified with, one that was isolated in the bladder, and it had not spread.

He went on to tell us this was a blind test, one in which neither he or us would know if I was

to receive the test medication or a placebo. We inquired, since I was not certain if I was going to get the medication, what the other options would be, were there other medications, other treatments that had proven effective, and he informed me that, really, there are no viable options. So naturally, I signed up for the clinical trial.

Surgery took place. The original diagnosis that the tumor was isolated to my bladder held true, and I was treated with the test medication. I had a post-surgical protocol of having cystoscopies every three months for the two years, then every six months, and to this date, once per year, the latest of which was July, just this past July. And I have been cancer-free since the initial removal of the tumor.

Four years, it was four years following this surgery, almost to the day, I received a letter in the mail, and it really wasn't on my mind, but it said that I did receive the test medication, the study medication, apaziquone, during my participation in the clinical study. To that time,

I did not know if I had got it.

I told my wife about the letter, and we were both thrilled that I had received the medication rather than the placebo. I was grateful to have had that test medication certainly, a medication that has kept me, I believe, cancer-free.

I have not had to endure the emotional and physical pain, or the financial consequence and burden of subsequent surgeries, which are no fun. The cystoscopies are no fun at all, but the surgery was less fun.

Knowing that I did receive apaziquone, and given the cancer has not returned, as far as I'm concerned, the treatment was effective in preventing a recurrence of my bladder cancer.

Thank you for the opportunity to share my experience with you. We talk about clinically meaningful, and I don't know if one person is clinically meaningful, but to me it certainly is. That's all I have. Thank you.

DR. ROTH: Thank you.

Speaker number 2, if you'd introduce

yourself and any organization you represent, and any relationship to the sponsor.

(No response.)

DR. ROTH: Okay. Speaker number 3?

MR. SILVER: Good morning. My name is Ed Silver. I live in North Myrtle Beach, South Carolina. I'm 73 years old, and I have bladder cancer. I was a smoker, quitting in 1986. I have no financial relationship with Spectrum at all.

My urologist, Dr. Glenn Gangi, discovered my cancer in 2011 when he removed a very large and extremely painful kidney stone. After removing of the stone, he gave me a good news and bad news scenario. The good news being the successful removal of the stone. The bad news was that he discovered a low-grade carcinoma cancer in my bladder.

He had removed the tumor during the kidney stone operation. A year later, the cancer returned. A TURBT was scheduled. This TURBT is performed in an outpatient surgeon facility, taking your vitals, EKG, in a gown, wheeled in, given

anesthesia, put in the stirrups. The surgeon enters a scope through the urethra, cuts out and cauterizes, then sent to pathology.

I have had six TURBTs in five years. After each procedure, you experience a burning sensation along with bleeding for two days to three days afterward. Initially, you're urinating pink, and day by day the blood dissipates.

After my second TURBT, I asked Dr. Gangi about my options. He gave me three. One, BCG; two, chemo/radiation; and three, the surgical removal of my bladder. Being the lesser of three evils, we proceeded with BCG.

BCG consisted of six weekly infusions through the urethra into my bladder. After each infusion, I had to lie still for one hour, change positions every 15 minutes, side to side, front to back. Then I was able to relieve the bladder of this pressure.

For two days afterwards I experienced painful burning every time I urinated. Also, I had a low-grade fever combined with difficulty

controlling the urination process, which means I couldn't go too far from a toilet. If I had to go, I had to run. This means that I was homebound, couldn't go anyplace or do much of anything. Three months later, the low-grade cancer had returned. This means another TURBT and a second round of BCG in 2013.

In October, they found a more aggressive carcinoma in situ. After the second round of BCG failed, Dr. Gangi and Dr. Karr, my primary care physician, began discussing the possibility of bladder removal and spending the rest of my life wearing an ileostomy bag for urine collection. I was encouraged to do my own research and join into a bladder cancer online support group. I had a very tough time with this.

For the last 13 years of my working career, I traveled extensively throughout North America as a national sales manager for a Fortune 500 company. I was so looking forward to retirement and catching up on my golf, and playing as much as I could. I get the news, I have bladder cancer, and the

possibility of wearing a bag on my side for the rest of my life was very hard to accept. I spent many sleepless nights mulling over this removal of my bladder.

I went for a second opinion to the University of North Carolina at Chapel Hill. They wanted me immediately to enter a BCG six-week program. Explaining that I already had two six-week sessions with negative results, they offered that this is their standard protocol. I returned to Dr. Gangi, and he said he wanted to discuss my case with Dr. Neal Shore, director of Carolina Urologic Research Center in Myrtle Beach.

In November of 2013, I entered an open-label clinical trial, which continued for 10 months. The next four cystoscopies were clear, but in January, they found a new low-grade carcinoma. In February of this year, I joined an immunotherapy vaccine trial. My last cystoscopy was clear. I wonder how long it will be before my next reoccurrence.

We need more treatment options. Current options are BCG, chemotherapy, bladder removal. In

a great country such as ours, the most powerful country in the world, a country capable of putting a man on the moon, why are there so few options for people suffering from this dreaded disease?

To summarize, if everybody in this room, especially those on this side of this black panel right here, experienced a TURBT, I'm sure a greater emphasis would be put into this area for other options. Thank you.

DR. ROTH: Thank you. Speaker number 4?

MS. MADDOX-SMITH: Good morning. My name is Andrea Maddox-Smith, and I am the CEO for Bladder Cancer Advocacy Network. I have no financial relationship with this organization.

I am pleased to be here representing the Bladder Cancer Advocacy Network, which we so fondly call BCAN, and the nearly 77,000 people who will be diagnosed with bladder cancer this year. Bladder cancer is the fifth most common cancer in the U.S., yet it does not rank as high on the list for federal research funds.

Public awareness of this disease is low, yet

it is estimated more than 500,000 Americans have the disease, and another 16,000 will die from bladder cancer this year alone.

A bladder cancer diagnosis has an enormous physical, emotional, psychological, and an economic toll on patients and their families. For non-muscle invasive bladder cancer, the initial treatment is the removal of the tumor through a cystoscope using a procedure called transurethral resection of the bladder tumor. This is often followed by adjuvant therapy, which can reduce the chances of the cancer recurring.

But bladder cancer is a disease with a high rate of reoccurrence. For most patients, bladder cancer requires regular and invasive surveillance every few months using a cystoscope inserted into the urethra to provide a way to examine the bladder wall.

You've heard today from experts, and now from patients, about just how invasive this is. Roughly 20 to 25 percent of initially non-muscle invasive cancers will progress to invasive types

during the person's lifetime. For the remaining 30 percent of bladder cancer diagnosed when they are muscle invasive, most patients require surgery to remove the bladder and surrounding organs. Additionally, a urinary diversion to allow that individual to void must be created for the patient to live.

BCAN is not a medical organization. We are a patient advocacy organization. We raise awareness of the disease and provide education and support for the bladder cancer community. BCAN applauds and encourages research into the safe and effective new ways of diagnosing and treating this disease, and we work to advance bladder cancer research.

Unlike most major cancers that have seen scientific advances in treatment in the past 30 years, bladder cancer patients' options have been limited. Finally, we want to emphasize the need for FDA to fully explore options that demonstrate safe and effective treatments through clinical trials. Additional treatment options for

bladder cancer are desperately needed. Thank you.

DR. ROTH: Thank you. Speaker number 5?

MS. O'HEARN: Good morning. My name is Michaela O'Hearn. Spectrum has paid for my travel and hotel. Thank you for the opportunity to tell you a little bit about my life with recurring bladder cancer.

In May of 2009, I woke up in the middle of the night with a screaming bladder. When I went to the bathroom to relieve myself, nothing happened. After what seemed to be forever, I was able to go. Even though this incident frightened me, I told myself it was a fluke and delayed seeking treatment for several months. When I found myself rocking on the toilet to go, I knew I had to do something. A visit to my doctor resulted in several tests and referral to a urologist.

On December 1st, 2009, I underwent surgery to investigate a mass in my bladder. I woke up in a hospital room to be advised that the mass was cancer. The doctor told my family he had removed a tumor about the size of a peach, and the bladder is

about the size of a grapefruit.

As I tried to absorb this and shake off the effects of the anesthesia, I was visited by the doctor's physician assistant who in essence told me I would most likely lose the bladder. I spent the next 48 hours in the hospital needing assistance to walk, because the anesthesia left me dizzy and unbalanced, watching a catheter bag fill up with what resembled cherry Kool-Aid, putting on a brave face for my family, and crying in the dark each night.

In the 6 and a half years since then, I've quit counting the number of BCGs, mitomycins, and TURBTs I've undergone. Since everyone here is familiar with BCG treatments, I will simply give you a patient's perspective.

In an exam room, you are asked to disrobe and take a frog leg position on a narrow table. The nurse preps the area with a numbing gel, and that gel is cold enough to bring your backside up off the table. A successful installation might burn a bit, but the discomfort has just begun.

The medication is held in the bladder for two hours, and then the toilet must be bleached after each use. The side effects for me include urgency for the next 12 hours. Sometimes I can't wait for the 15 minutes for the bleach to take effect. Bladder spasms similar to dry heaves; they bend you over. Discomfort trying to sit, red chapped hands from frequent washing, and the overwhelming desire to lie down when I find myself nodding off on the toilet.

After a round of BCG, there are the TURBTs. These eat up vacation days, cause family and coworkers to change their schedules. For me there is the anxiety of another IV, having my arm strapped down in a surgical suite, and waking up with the room spinning.

I've dealt with clown marks on my face, a tearing cough, nausea, dizziness, a chipped tooth, going home with a catheter, and post-surgical bleeding and constipation. My worst memory is waking up with a tube still in my throat feeling like I was suffocating.

Whenever possible, I opt for an office fulguration. A lidocaine solution is placed in the bladder that lessens but does not eliminate the discomfort. Each time the doctor steps on the instrument, you feel a point of discomfort that blossoms and grows. I liken it to a lightening globe, and your bladder is the globe.

Although I feel every zap, I feel a little bit of pain is worth reducing my medical bills. And on the bright side, there is no IV, no anesthesia, and no catheter.

I don't talk about my cancer anymore. People get uncomfortable and tend to stop conversations. In the last 6 and a half years, I've learned to pee and relax on cue. I've also learned that for all the well wishes and prayers, in the middle of the night while everyone else is sleeping, cancer patients fight their inner battle alone.

These procedures and the anxieties that come with them have become the norm in my life. I live with them because I cling to the hope that someday

someone will come up with a treatment to stop these tumors from recurring. I would like to think that being here is a step in that direction, and my chance to help others in similar circumstances.

Patients need alternatives. They need safe and effective drugs. For the patients like me who have undergone procedure after procedure, I ask that you recommend that apaziquone be approved. Thank you.

DR. ROTH: Thank you. Our final speaker, speaker number 6?

DR. CONCEPCION: Dr. Roth and committee, good morning, and thank you for the opportunity to speak. I'm Raoul Concepcion. I'm a urologist in Nashville, Tennessee. In terms of financial disclosures, the sponsor has paid for my travel expenses. I do clinical trials. I am not involved in 611 or 612. I'm not a KOL for the company, nor do I receive any honorarium.

I'm going to make my comments really based upon a couple different perspectives. One, probably least important, is as a clinical

scientist and as a urologist, and probably number two, probably the most important, is as a patient advocate. I've been in practice for over 26 years. My primary clinical emphasis is urologic oncology.

So one observation, there was a lot of discussion about efficacy of the drug. Is this drug efficacious? Is it better than a placebo? So I think you do have some data in your slide deck. In slide CE-6, the company did do an efficacy marker lesion where they instilled drug in patients that had existing tumor, and there was a complete response rate. And I think that gives you some clinical data that this drug is active. You know, this is better than giving nothing.

Secondly, and probably more importantly, is that, like many tumors, I think Dr. Karsh said it appropriately, bladder is 10 years behind prostate, prostate is 10 years behind breast and colon.

We know phenotypes. We know non-muscle invasive bladder cancer. We know muscle invasive bladder cancer. But we have no biomolecular markers. We have no idea who's going to progress.

We have no idea who is going to respond to neoadjuvant chemotherapy for muscle invasive bladder cancer, who's not going to respond.

So this concept of taking all non-muscle invasive bladder cancers and lumping them together, until we have better genotypic markers, we have no idea.

Also as a clinician, Dr. Lerner appropriately stated that there was a study based out of the folks from the University of Michigan that talked about judicious use of intravesicular chemotherapy. My practice was one of those. We had 75 percent. We didn't have 100 percent because we couldn't get the drug. We couldn't get mitomycin. And as many of you know, mitomycin and BCG are in tremendous shortage the past couple years. The toxicity of those drugs are tremendous.

So yes, there are those of us that actively treat this. We try to follow the guidelines, but we need more therapies. We need more therapies that are efficacious. We need more therapies that are available.

So, from a clinical standpoint, from a clinical scientist standpoint, this drug, I believe, really could provide a lot of benefit for the patient, and more importantly from a patient advocacy standpoint.

I'm not a biostatistician, nor would I ever claim to be, nor do I think I ever want to be. But I think most importantly the question comes up, what is a clinically meaningful number. The FDA has come out and said, what's clinically meaningful?

Well, clinically meaningful is 1. I mean you've heard from these patients. In the era of precision medicine, it's 1. If you're the patient that has the threat of a recurrence, that has the threat of becoming progressive, and like Dr. Lerner said is that we don't know who's going to progress, but if that threat is always there, and we don't know, we don't have a marker to predict, the number is 1.

Dr. Shore stated that -- and again, there was some argument about what is the actual number

in terms of cutting down the number of TUR bladder tumors. It could be 1 percent, it could be 6 percent.

Again, as somebody who is also very much involved as physicians in the post-macro world, as we go from volume to value based medicine -- so you take 20,000 TUR bladder tumors, and just a guess, let's just say 10,000 per event, that's $200 million a year annually, just to reduce the number of TUR bladder tumors; not to mention the number of cystoscopies; not to mention the number of office visits; not to mention the loss of patient quality of life, reduction in work time.

So I would venture to say that this drug is efficacious. I would advocate for its approval, and thank you for your time.

Questions to the Committee and Discussion

DR. ROTH: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

We will now proceed with the questions to

the committee and panel discussion. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. So if the agency would like to read the question.

DR. ISON: So we ask the committee to vote, has substantial evidence of a treatment effect for apaziquone over placebo been demonstrated? And then go to the next slide, please.

For discussion, for those who vote yes to the first question, that an effect has been demonstrated, please discuss the clinical meaning of the results of study 611 and 612.

DR. ROTH: So just to be clear, we're going to vote once, not twice here. And if you vote no on the first, there's no relevance to the second question. And if you vote yes to number 1, then as we go around the table and you explain your vote, if you voted yes, then say, secondly, what you think the clinical meaningfulness is of this magnitude of benefit.

Are there any questions or comments about the way the questions are phrased, or any suggestions?

(No response.)

DR. ROTH: Okay. We'll open the discussion now before taking a vote. So, again, if you'd raise your hand, and Lauren will take down your name. Go ahead, Dr. Taylor.

DR. TAYLOR: Some of this is a little bit new to me. I tend to live more in culture dishes and animal models and phase 1s. And I would be remiss to design phase 2 and phase 3 studies because if you don't hit your question exactly, your results may not give you what you're looking for. So, if we could look at, I think it's FDA slide 20.

In both studies, we do cross zero, but the median dot is well to the right, suggesting favoring treatment. And to a non-statistician, this would suggest the risk of a type 2 error. And if this is potentially a type 2 error and we got a larger patient population to reduce those error

bars, if we're looking at that as a potential error, is not a meta-analysis with heterogeneity tests an acceptable way to potentially circumvent this, or look at it in a different manner?

DR. ROTH: Dr. Logan?

DR. LOGAN: So the point is that the study may be underpowered here for a 6 percent difference, and then you have maybe a type 2 error as a result of that. But we can't really figure out if it's a type 2 error or there really isn't a difference. Without additional data, you really can't make that determination.

So I don't think we should speculate on what might have happened if we had enrolled more patients and had a bigger trial.

Then whether the meta-analysis salvages that, the issues of it not being set up a priori in advance and things like that, it's kind of an attempt to salvage that. And as a result, you don't get the same kind of control of your false positive rate.

DR. ROTH: Dr. Haylock?

DR. HAYLOCK: I was just trying to figure out how to say this. Serving on this committee for a while, I have learned to respect the science of the process and how FDA goes about making these decisions. But in this case, I've also been an enterostomal therapy nurse who has spent a lot of years taking care of people with ostomies, and bladder cancer, and colorectal cancers, and other things.

I think it's sad and appalling that there's been not much done in this entity from a research perspective and a therapeutic perspective, and I really have to applaud this company for taking on what could be kind of a thankless endeavor.

I guess in this discussion, I understand -- well, I obviously don't understand all the statistics, but I do understand the meaning of statistical significance. But the question of clinical value, or clinical -- I can't remember what the word was, meaningful, clinically meaningful, I don't understand that because we just heard that it's been very clinically meaningful to

some people, and these people are representing probably hundreds of thousands of others too.

So the clinical meaningful discussion is going to be the tricky part here I think.

DR. PAZDUR: If I could answer that, because this is -- to put it in regulatory context, clinically meaningful, we're talking about a positive risk-benefit analysis; do the benefits of the therapy outweigh the potential risk to the patients?

But as we stated here, we can't get into the discussion of a risk-benefit analysis unless we are confident that there is a treatment effect here. That's why we phrase these questions, or put them in that order. And only to talk about a positive risk-benefit or a clinical meaningfulness is if you have decided that there is substantial evidence that there is an effect here.

As I stated before, we don't have to have a comparative effect to other drugs; it is there an effect, and then that has to be placed in the context of a risk-benefit analysis.

I've heard many comments being made here, and from the agency's point of view, we really do want to say that we really realize that there is a need for drugs. But as has been expressed by the open public hearing, these drugs should be safe and effective. It shouldn't be safe and maybe effective, or safe and I wish it was effective.

There is a regulatory obligation that the sponsor has to provide substantial evidence of safety and efficacy here. And here again, there are issues here of -- we all wish that we had better drugs. We, from the agency's point of view, have really made a committed effort in a dialogue with the urology community to try to foster development of these drugs.

So we're all on the same page here. And I really want to make sure that the American public understands that we realize that there is a need for safe and effective drugs. But first of all, we have to demonstrate, is there an effect here, and that usually comes from a statistical paradigm that has been set up and has been really orchestrated in

a logical fashion here rather than ad hoc hypothesis-generating analysis.

Then the context of is this 6 percent, or whatever this percent would be is clinically meaningful, would then occur after the effect has been demonstrated, after you have substantial evidence of that effect. And that's why we're asking the questions in these two situations.

DR. ROTH: Dr. Jennifer Taylor? Ms. Speers?

MS. SPEERS: Well, I hate that the risk-benefit comes, or the harms-benefit comes after the decision of whether we really see the effect type of thing. I'm here on a patient representative. My mom had bladder cancer, and had the TURBT, and had mitomycin C, and really suffered from the side effects, I must say.

She's also a breast cancer survivor, and I think the bladder cancer has really affected her quality of life much more. And it was eight years ago, and she still suffers from side effects from that. Even without a recurrence, she has suffered from the drug.

In reading this, it really was very conflicting to me that there are treatments out there, possibly like the mitomycin, but it's so toxic for the minimal benefit, and it's not used by many people, yet you have a recommendation to use it because it does reduce risk.

That leaves the patient feeling very confused. And I know my mom was like, well if I don't get it, I'm going to die, or it's going to come back. And there's that fear in the patient. I think I really appreciated hearing from patients actually, other patients that had different stories, because I think that is what we're really going about.

The patient burden in this disease is huge. It's bigger than any other disease that I can think of. And not only the physical burden, the psychological burden, but the financial burden. Because none of these drugs are approved. The finance comes back to the patient, and that is horrible for the patient. And the physical is horrible for the patient for this disease.

So there is such a huge unmet need for this. The recurrence rates are so high. Luckily, my mom has not had a recurrence. But putting that all in context, I mean, I really hope that this trial goes forward and proves to be very successful. It makes sense to go for the 30 minutes. It makes sense that there's less side effects because of the blood.

So I really think that in the harms-benefit thing, this drug is going to outdo any other drug out there because of the low toxicity. But then when you look at the data, and you know I was struggling with the 6 percent, and in the breast world, 6 percent would be great because we're at the 1 percent altar. But I think that looking at the data, there was that wiggle and the crossing the line, crossing the zero or crossing the 1 in the other analysis.

It's kind of a struggle because it's clearly on the side of benefit of some kind. We don't know what that is, though. And there is the possibility of being no benefit as well as being up to

12 percent if you look at the range. It's such a variability.

So I don't know, because of what's not known about bladder cancer, that you don't know why that variability is there, because they might be different in some respect that we don't know about yet because of the lack of knowledge about that, or if it is because of the study and because of the drug.

So I'm really struggling with that, but I think, whichever way I go, I think that the need is so much there for this disease. And I think the patient -- the burden on the patient is so high for this disease, it would be nice to have a drug with low toxicity that might actually prevent recurrence.

DR. ROTH: Thank you.

DR. PAZDUR: If I could just mention, you know many of you are new to this committee, and some of you are medical oncologists that have been on this committee. And we have had many applications that dealt with very far advanced

metastatic disease populations, and we have approved drugs simply on the basis of a single-arm study with a response rate, whether that response rate is 15 percent, 30 percent, whatever, is in the context of the disease.

When we have a response rate for that disease, in that specific indication, we know that there is a treatment effect there because the disease doesn't go away on its own, or doesn't shrink on its own. So that is substantial evidence.

This is a different situation here because you have basically curves, and therefore the need to rely on the statistics is much greater here. And we have to take a look at it in the context of the indication that is being proposed here, rather than very far advanced disease. They have not demonstrated this, any activity for far advanced disease in this setting, and they're not seeking that indication.

DR. ROTH: If I could just throw out a thought. Sometimes I get confused by the

percentages and relative reduction, 14, 15 percent, and those kind of numbers, so I prefer hard, whole numbers. So if you look at 611, 406 patients received drug, including 35 that had no tumor, for 9 fewer recurrences.

So when we talk about cost, we talk about toxicity, we need also to think about the patients who are not benefiting from the drug as well. Because the nature of this disease, and you don't have the histology, that means treating more people. So I think the burden is on us to prove efficacy.

Are there any other comments before we vote?

(No response.)

DR. ROTH: Okay. If there's no further discussion of this question, we'll now begin the voting process. We'll be using an electronic voting system for the meeting. Once we begin the vote, the buttons will start flashing, and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of

your vote, or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to.

So please press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. And again, if you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. TESH: For the record, the voting result is zero yes, 14 no, zero abstentions, and zero

non-voting.

DR. ROTH: Now that the vote's complete, we'll go around the table and have everyone who voted state their name, their vote, and if you want to you can state the reason why you voted as you did into the record. I think we'll start from this side for voting members.

DR. CHAMIE: So as a urologist, I really wanted to get a drug approved for non-muscle invasive bladder cancer. I think this drug will work. Unfortunately, based on the data that I've seen, I don't necessarily believe that they've demonstrated evidence of efficacy.

That said, I think they set the bar high, and I think in the future, with the phase 3 study, hopefully we'll get that approved.

DR. ROTH: Remember to state your name for the audio portion of the record. Thank you.

DR. LOGAN: Brent Logan. I voted no. So I look for robust, statistical evidence of efficacy in making that determination. Here, they did not meet their primary endpoint in either trial. The

subgroup analyses are ad hoc and can lead to potentially biased estimates of the treatment effect in the subgroups of interest.

The meta-analysis didn't have a prospective protocol, it was done post hoc, and it doesn't provide the same level of statistical certainty, or robustness, as the two separate trials, which would have met their primary endpoint.

Then the missing data issue also speaks to a lack of robustness, given the small estimated effect in these two trials. But I would certainly encourage the sponsor to finish their ongoing trial to hopefully better establish efficacy.

DR. TAYLOR: John Taylor, and I voted no. I'm a urologist, but I'm also a researcher. And I'm a tremendous patient advocate, and I do drug development and discovery and experimental therapeutics solely to try and bring something to my patients.

I think that this drug showed tremendous preclinical efficacy and efficacy in phase 1, 2. And someone said it, I think that it's not a

failure of the drug, it's a failure of the study design. And I really am hopeful that this will come back in another phase 3 that's designed properly and show efficaciousness, because we really need it.

DR. TAYLOR: Jennifer Taylor. I voted no. The secondary and post hoc analyses are very compelling, but the speculative interpretation of those analyses is not enough to justify the indication and then the hopeful widespread adoption of a practice in a population that already has a lot of risk, and worry, and concern.

Being a urologist and a patient advocate, I agree that this is a place where we need and want desperately for new solutions, and I am optimistic that with more evidence that can be reached with this drug.

DR. HAYLOCK: Pam Haylock. I also voted no. I guess not to be redundant to what everyone else has said, but I think the science has not held up right here. And I think, Dr. Taylor, you stated it perfectly, and hopefully the other design will be a

lot more compelling, and we'll get there.

MS. SPEERS: And I'm Patty Speers. I also voted no. I think it's very hopeful, and I really encourage the company to go forward. Because of the toxicity profile of this drug, it's very compelling, and the subset analysis were very compelling. You know, you don't want to give false hope to patients as well, so I think that the data just wasn't quite there.

DR. ULDRICK: Thomas Uldrick. I also voted no. I wouldn't consider apaziquone a promising drug. I think the biologic rationale, the preclinical data, the marker tumor studies, and the apparently superior safety, and the urgent clinical need all suggest that this is potentially a good drug for use.

However, benefit was not shown in either study, and the way that the pooled study was conducted did also not convince me. It was done post hoc. There was not a protocol specifically for it that addressed false discovery rate, that addressed missing data, that addressed possible

heterogeneity between the studies. So I'm not convinced that as administered the drug showed benefit.

Additionally, a large number of patients got drug administered in a way that seems to be inappropriate, and appropriate administration of the drug needs to be approved, or proven in the ongoing studies.

DR. RIELY: My name is Greg Riely. I voted no. I feel like this is clearly a very difficult area to develop drugs, and this is a very new type of trial design for this area. And I think it's really important that the stuff continue. But the way the drug was given here and the population it was given to, it's not clear that it helps people.

DR. RINI: My name is Brian Rini. I voted no. Like everyone else in the room, I agree there's clearly an unmet need here that affects a large number of patients. We need safe and effective drugs that are actually used, which are unlike maybe some of the currently available options.

I think one of the most compelling things I heard was that reduction in TURBTs and the sequelae could be clinically meaningful, even at the level of reduction that's estimated at around 6 percent in this study. I voted no because there's just too much statistical uncertainty here, as others have alluded to.

The missing data is a problem, even if it's at the 10 percent level. But the sponsor implied that's still greater than the estimation of treatment effect. I don't think you can put two negative trials together and make a positive in most circumstances. And the overlapping confidence intervals, both within the trials and in the pooled analysis, which is inherently flawed, as others have pointed out.

I think the subgroup analyses are interesting. I applaud the company for taking those hypotheses and actually prospectively testing them, and I'm as hopeful as anyone that those trials turn out positive.

DR. ROTH: I'm Bruce Roth, and I voted no.

I'm the person tasked at my institution of giving intravesical chemotherapy, and I would like nothing more to have additional active agents. So does this agent have activity? It's possible, but we can't approve drugs based on the possibility of effect.

So for me, what I was given was two negative phase 3 trials and asked to approve a drug. And I disagree with the pooled analysis, and I don't think that two trials, powered to detect a 12 percent difference when pooled, gives you the power to detect a 6 percent difference.

So as was said by Chip [ph] earlier on, it's possible that it could have been all the way down to 1 percent. But all we can tell is it's less than 12 percent, so I voted no.

DR. COLE: Bernard Cole. I voted no, largely for the reasons that have already been mentioned. I do believe that there is some evidence of effectiveness, it's just that it does not reach the substantial bar that's required for approval.

DR. PAPADIMITRAKOPOULOU: Vali Papadimitrakopoulou. I also voted no. And beyond all the arguments that were already discussed from others, I agree with those. I think the drug has demonstrated activity in marker studies, and I think the agent is safe. And I think it is good that the company is proceeding with additional trials.

I would like to add the comment that the urological community likely needs to define the endpoints for these types of trials a little better, based on all the meta-analyses and what has been done so far, so that actually large randomized studies are not performed with an unclear primary endpoint goal because, to me, it still remains unclear why the 12 percent was chosen.

DR. NOWAKOWSKI: My name is Greg Nowakowski, and I voted no. I will start from complimenting the sponsor for conducting really well designed studies. Those studies are difficult to do. They require a lot of follow-up and procedures on the patients. And despite some missing data, the

studies were actually well done.

Regardless though, both studies did not show statistical significant difference over a control arm, so they are negative studies. And unfortunately two negatives in this case will not make it a positive study because there's very limited methodology how this pooled analysis could be done at this point.

To this point of the pooled analysis and how we can trust it, right now, it appears from the opinion of our expert statisticians there is no really methodology to combine such a phase 3 studies if there was not a predefined analysis done when the studies were designed.

But I expect, as we're going into the future, we may actually encounter a similar situation that somebody has marginally positive phase 3 studies. And I would assume with a work of statisticians, some methodology of how to interpret this data could be developed looking at pooled analysis from many different clinical trials over time. But as of now, such methodology does not

exist; hence, the efficacy could not be demonstrated, which would be statistically significant. Hence, my vote, no. Thank you.

DR. GONZALGO: Mark Gonzalgo. I voted no. As a urologist, I mentioned this earlier, it would give me no greater pleasure and satisfaction to be able to offer a new novel agent to my patients that has demonstrated substantially that it is better than not doing anything at all. And as a scientist, the evidence was not compelling enough, even at the 6 percent threshold for me to vote, or to change my vote to a yes based on the data that was presented.

DR. ROTH: So, just to summarize for the record. It sounds like it's a consensus of the committee that it's primarily a lack of the ability of the design of the trials, and the ultimate endpoints to prove efficacy.

Not saying that there's not, looking forward to additional information from the sponsor, and particularly the phase 3 trial that has been outlined. And certainly if efficacy can be shown,

then would love to see the drug back again before the committee. But based on what we have today, there was not sufficient reason to approve that.

Any other comments?

(No response.)

Adjournment

DR. ROTH: I will now adjourn the meeting. Panel members, please leave your name badge here on the table so it may be recycled. Please take all personal belongings with you as the room is cleaned at the end of the meeting day. Meeting materials left on the table will be disposed of. Thank you.

(Whereupon, at 11:57 a.m., the meeting was adjourned.)