Synergo system consists of two separate components, the Synergo hyperthermia device and the Synergo kit. The Synergo hyperthermia device is a computer-controlled device that monitors and controls treatment and contains the user interface. The Synergo kit contains single use components required to perform each Synergo treatment, namely the disposable catheter tubing set and two vials of the mitomycin C, both of which are packaged sterile. The catheter tubing set consists of a specialized urinary catheter used to deliver treatment and tubing to circulate the drug solution in and out of the bladder during treatment.

The vials of mitomycin C are provided in the clinical dosage specified in the Synergo system labeling. Mitomycin C is provided to Medical Enterprises in final package form from the drug manufacturer, Bedford Laboratories. Mitomycin C is legally marketed in the United States for a different indication and route of administration and is sold by Bedford Laboratories under the trade name mitomycin for Injection, USP.

By copackaging the drug with the device disposable components, the firm is meeting FDA's requirements for mutually confirming labeling.

Specifically, the labeling insert package with the Synergo kit is intended to provide the user with adequate directions for use of both the device and drug components.

The sponsor proposes that the Synergo system be indicated to deliver heat transurethrally by means of radio frequency energy to the urinary bladder walls for the treatment of superficial transitional cell carcinoma of the bladder or STCCB, concomitant with intravesical installing of Mitomycin for Injection, USP. The combination of Synergo and mitomycin C is intended for the prophylactic treatment of recurrence in patients following endoscopic removal of Ta and T1 and grades 1 through 3 STCCB. Synergo and mitomycin C treatment is clinically indicated for STCCB patients of intermediate and high-risk.

FDA has conducted a very comprehensive review of this PMA. Since this is a device/drug combination product, our review has spanned to two centers, the Center for Devices and Radiological Health and the Center for Drug Evaluation and Research. Additionally, the Office of Regional Operations was involved to perform bioresearch monitoring inspections which are FDA's clinical data

audits.

I'd like to take a few moments to acknowledge all the individuals that continued to the review of this PMA. In addition to myself as Team Leader, this slide lists the clinical reviewers as well as Janine Morris, who until recently was Chief of the Urology and Lithotripsy Devices Branch.

The reviewers listed on this slide reviewed the statistical information, pharmacokinetic data and post-approval study plan.

These individuals reviewed the preclinical testing information and patient labeling.

And these individuals, they reviewed the sterilization information and manufacturing process or conducted or oversaw the bioresearch monitoring inspections.

The principle of operation of this combination product has already been presented in detail by the sponsor. Briefly, Synergo treatment involves hyperthermia of the internal urinary bladder wall with circulation of an intravesical dose of the chemotherapy drug, mitomycin C. The hyperthermia device heats the bladder wall using radio frequency energy, specifically in the microwave range, delivered from a catheter-based antenna.

In addition to the antenna, the specialized transurethral catheter contains five thermocouples, three in the patient's bladder and two along the catheter shaft to provide temperature feedback to the system, as well as internal lumens for the continuous circulation of the drug solution between the bladder and an external heat exchanger. The treating physician adjusts both the radio frequency power output and drug circulation flow rate to maintain the temperature of the bladder wall in the range of 42 plus or minus 2 degrees Celsius.

Treatment is initiated following transurethral resection of all tumors. A complete course of treatment consists of eight weekly inductive sessions followed by four monthly maintenance sessions. Each treatment session lasts 60 minutes. AS previously stated, the physician controls the hyperthermia system to maintain a temperature of 42 plus or minute 2 degrees Celsius at the bladder wall. Prior to the session, the patient's bladder is drained, local anesthesia is given along the urethra, and the treatment catheter is inserted into the bladder. Mitomycin C is administered in 2 consecutive instillations of 20 milligrams in 50 mL distilled water, each for a dwell

time of 30 minutes. At the end of the second 30-minute period, hyperthermia is terminated, the patient's bladder is emptied, and the catheter is withdrawn.

This slide lists the preclinical tests that were performed to evaluate the safety and functional performance of the Synergo device. The sterilization and manufacturing information was reviewed from both a chemistry, manufacturing and controls perspective in the Center for Drug Evaluation and Research, and a good manufacturing perspective in the Center for Devices and Radiological Health.

FDA has no major concerns regarding the preclinical data provided. As noted in the FDA Executive Summary, minor issues remain regarding the claimed shelf life of the Synergo kit.

There are several sources of clinical data provided for review in the PMA, all of which were collected at sites in Europe and Israel. The table presented here lists the data sources that were collected in prospective clinical studies as well as the supportive clinical data. I would like to bring your attention to Study 101.1, highlighted in yellow in this table. As you heard, this is a randomized clinical trial intended as a pivotal study dataset in

support of the safety and effectiveness of the Synergo system. In this study, eligible subjects were randomized to either Synergo treatment consisting of hyperthermia plus mitomycin C or mitomycin C alone. The main effectiveness analysis for this study is comparison of the two-year rate of recurrence of bladder cancer between study arms. Safety is evaluated by analyzing the incidence and severity of adverse events.

The remaining sources of clinical data were submitted to provide supportive data regarding the safety and/or effectiveness of Synergo treatment. For various reasons, these studies are not intended to provide pivotal evidence of the safety and effectiveness of this combination product. Specifically, the human pharmacokinetic study was conducted to evaluate the systemic levels of mitomycin C during Synergo treatment. Study 102.1 reports the results of an unplanned interim analysis of an ongoing study comparing Synergo treatment to Bacillus Calmette-Guerin or BCG. And, Study 101.4 is an exploratory study performed to assess the use of the Synergo system in a different patient than specified in the PMA's proposed indication.

The other clinical data sources provided in

the PMA, and listed on the law row are comparisons to historical mitomycin C and BCG data reported in the literature, commercial data collected on the Synergo system and reported as the European Prophylactic Study and data from Bladder Salvage and European Ablation Patients, collected at European sites to evaluate different indications than posed in the PMA.

FDA's review comments regarding this clinical information will be presented later by Drs. Kane and Li.

To understand how the pivotal study data and patients were managed, it is important that I briefly discuss the chronology and progress of study events.

Study 101.1 did not originate as a planned study to support a marketing application in the U.S. The protocol for the study was originated in 1993. In 1997, the study sponsorship was transferred from one of the study sites to Medical Enterprises or MEL. That same year, MEL's investors contracted with SMS, a British firm, to create case report forms and conduct monitoring visits. During the monitoring visits conducted in 1997, the case report forms were retrospectively completed by transcribing existing data from the patients' medical records. After the

1997 monitoring visits, the case report forms were completed prospectively.

Following study completion and preliminary discussions with FDA, MEL submitted this PMA in August of 2001. FDA conducted its in-depth review of the PMA in the summer and fall of 2001, and additional in-depth review cycles occurred in 2002 and 2004 following the firm's submission of additional information. Due to the unconventional way in which the case report forms were developed, FDA determined during the 2004 review cycle that additional review of the PMA should not proceed until the clinical data were audited and bioresearch monitoring inspections.

Based on the firm's availability, FDA conducted these inspections of all sites in late 2005. These inspections verified that the data contained in the case report forms and PMA data listings are accurate reflections of the investigator's source documents. However, limitations to the use of retrospectively created and transcribed case report forms include the potential for relevant, pre-1997 study data not being collected in the patient records and the potential for recall bias.

This slide outlines the remainder of FDA's presentation. I would now like to introduce Dr. Herrera, who will give a clinical overview of bladder cancer and current treatment options.

DR. HERRERA: Good morning. I'm Hector Herrera, the urologist for the Urology Devices Branch. I'm going to talk about bladder cancer. All the Panel members are experts in this subject. So this presentation is given for the benefit of the public not familiar with bladder cancer.

More than 60,000 cases annually are diagnosed in the United States. The main causes is tobacco use, industrial carcinogens and in general, the aging of the population.

The most common pathological subtype is the transitional cell carcinoma or TCC. It's observed in over 90 percent of the tumors. Squamous cell carcinoma is 5 percent and adenocarcinomas approximately 1 percent.

The prognosis factors for the bladder cancer are two, the stage and grade. Stage is how far the disease has spread, and the grade is the appearance of these cells to the microscopic examination.

The tumor stages of the non-muscle invasive

bladder cancer is Ta, T1 and Tis or CIS. The Ta is invading the urothelium, the T1 invading the urothelium and the lamina propria and Tis is confined to the mucosa but this tumor is highly malignant and aggressive and as I say before is called also CIS.

We have the representation of the bladder wall in this slide. Here we have the urine in contact with the mucosa, then urothelium followed by the lamina propria, the muscle cells, the fat and the peritoneum. We have here what is described as TIS, is a very superficial tumor confined only to the mucosa but is very aggressive. The Ta invades the urothelium and the T1 invades the mucosa, urothelium and doesn't go into the three layers of muscles that involve the bladder.

The tumor grade as I said before is the appearance of the cells to the microscope and is divided in well differentiated, moderately differentiated and poorly differentiated.

We can see an example of what is a well differentiated, we have here in the bottom, the normal cells of the bladder and on top is the increased number of cells but as you're noticing here, the architecture is almost the same.

In the moderately differentiated, we notice

that we have a lot of the architecture but we can see perfectly well each cell.

In the poorly differentiated, we cannot distinguish anymore the cells. That's why it's called poorly differentiated.

The treatment options, the main one is the transurethral resection of the bladder tumor. Then there is the intravesical chemotherapy or immunotherapy or intravesical laser ablation and photodynamic therapy.

Basically taken to the operating room and the bladder tumor is resected. This is called TURBT or transurethral resection. It's essential for the diagnostic of the tumor but you need to be deep enough to get a sampling of the first layer of muscles.

The most commonly employed intravesical agents in the USA is the Bacillus Calmette-Guerin or BCG and the mitomycin C.

The mechanism of action, BCG is inflammatory host response with release of special proteins, that they are called cytokines. The mitomycin C is antineoplastic, inhibits DNA synthesis. Both are used as adjuvant or maintenance fashion.

The mitomycin C usually is given between 20 to 60 milligrams instilled in the bladder and dissolve in distilled water most commonly.

And the BCG is the first line of treatment for the Tis. It's effective as prophylaxis for recurrences but the optimal dosing has not yet been established.

There are side effects for both of them. The mitomycin C, the rate is 22 to 24 percent with multiple does with or without maintenance. The main side effects is urgency, frequency, urethral infection and bladder contracture.

The BCG, 38 percent with induction and 57 percent with induction plus maintenance. Side effects, fever, chills, malaise, altered liver functions and sepsis.

The recurrence and progression rates after resection, the recurrences are decreased by 31 percent with BCG maintenance and by 18 percent with mitomycin C. The progression rate estimate in all patient risk groups is 8 percent for BCG and 4 percent for mitomycin C.

The predicting factor, they are divided in three, the low risk, the intermediate risk and high-risk, according to the European Urology Association

and is based on the number of tumors, the size of them, the prior recurrence, the T category, tumor grade and the presence of Tis. Thank you very much.

DR. KANE: Good morning. I'm Robert Kane. I'm a Medical Oncologist, and I'm a Clinical Reviewer in the Center for Drug Evaluation, CDER. I will be presenting the clinical review of the Synergo application this morning.

I will discuss superficial bladder cancer briefly to relate Dr. Herrera's discussion to the Synergo application. I will then discuss regulatory considerations for marketing. I will discuss certain of the Synergo studies, 101.1 in particular, and 102.1, and conclude with some regulatory concerns.

For non-muscle invasive disease, superficial bladder cancer, as you have heard, primary therapy is cystoscopic complete removal. Pathologic staging and grading is extremely important to established prognosis and additional treatment options, which may include adjuvant drug therapy intravesically into the bladder and you have heard that BCG is FDA approved for this indication. Mitomycin C, Interferon and other agents have been employed.

You have also heard the population is

heterogeneous and thus outcomes vary. Recurrence is common. Progression is less common and not apparently altered by our therapies to date. Prognostic factors affect this, and these have been discussed as well. And thus, standard of care has been complete resection, observation, and repeat of the procedure, and recurrence after TUR alone has been estimated anywhere from 10 to 70 percent by 2 years based on the characteristics of the patients examined. And, adjuvant treatment is indicated for the higher risk patients.

I will abbreviate some of the comments from these slides because you already know them and have heard them enough times I think.

With intravesical treatment with mitomycin C, either as immediate following cystoscopy and TUR or maintenance, there appears to be an overall suggestion of a reduction of about 18 percent in the probability of recurrence over the 2 year time interval. Again, there's considerable variation in this information.

While mitomycin C is not FDA approved for the treatment or prophylaxis of superficial bladder cancer, it has wide usage for this condition. And you've also heard already about the availability of

BCG under these conditions, and I think we would all agree that much additional improvement in the management of this condition would be very desirable.

The study endpoints that have usually been examined for this condition include recurrence and recurrence by the two-year time interval has commonly been used. Progression, indicating advancement of the T stage, as mentioned, is generally unusual unless there's high grade disease present.

Recurrence-free interval or time to recurrence, time to event endpoints may be utilized. Long-term outcomes, however, have not been systematically studied for this condition.

Turning now for a moment to consider requirements for marketing approval, we look for reasonable assurance based on valid scientific evidence demonstrating effectiveness with acceptable safety. And the source of this evidence should be adequate and controlled investigations. In addition, other types of studies can provide evidence as well.

Now, this slide indicates what we might classify as ideal characteristics for a single study to support effectiveness. It should be multicenter. It should be adequately powered. There should be consistent efficacy across multiple endpoints and key

study subsets. The statistical results should be very persuasive, and the study should be clinically compelling for the benefit to the risk assessment.

Turning to the Synergo application, this represents a device and drug combination product as has already been described. And the proposed indication is for use for the prophylactic treatment of recurrence following endoscopic removal, and patients should be considered to be at intermediate or high-risk for this to be applicable.

I will be commenting on the following four studies submitted by the sponsor.

With respect to Study 101.4, titled the tumor ablation study, patients enrolled in this study were those who were not fully resectable. It's a single-arm evaluation of the Synergo device plus mitomycin C.

Study 102.1 is a randomized comparison of Synergo plus mitomycin C versus BCG alone without the use of hyperthermia. Patients had to have definitive TURBT, and this study began in 2002. It consists of six weekly inductions and then six months of maintenance once a month. Four different types of BCG are being used in this study. The planned enrollment according to the applicant is 300, and

based on a data analysis performed in April 2007, at this time, we've been informed about 90 evaluable patients accrued over 5 years at 10 different sites. And the Synergo plus mitomycin C arm is of interest for safety.

The applicant has identified Study 101.1 as their pivotal study, a comparative study of intravesical mitomycin C instillation or mitomycin C and local hyperthermia for the prophylaxis of a recurrence of superficial transitional cell bladder carcinoma. As you have heard, the study was conducted at three sites. This began as a research collaboration among the sites. Enrollment between 1994 and 1999, and during this time interval, 83 patients were accrued and randomized. You've also heard case report forms were initiated in 1997.

And according to the plan, patients were to be randomized one to one between Synergo hyperthermia at 42 degrees plus mitomycin C which was preheated versus mitomycin C alone which was administered at room temperature, and 2 successive instillations for each patient were used. Patients received each over 30 minutes projected dwell time, and thus a total exposure time was to be 60 minutes for each treatment. All patients were to receive eight weekly

cycles and then monthly times four. Cystoscopy was to be performed after the initial eight weeks and then quarterly.

And patients on the Synergo arm, since the catheter was retained in the bladder, had the bladder drained via the catheter after the one hour hyperthermia treatments, and in the protocol, the treatment could occur between a time interval of 40 to 75 minutes. So it was considered reasonable. Patients on mitomycin C alone were instructed to void spontaneously after the total of one hour, and treatment was to being 20 to 40 days after the definitive resection, with quarterly follow-up to include cystoscopy, cytology, biopsy of any suspicious areas until two years or recurrence. If recurrence occurred, patients then went off study.

In the 1993 protocol, several endpoints were stated without development of the hierarchy or specific identification of what was to be the primary endpoint. And these endpoints included disease-free interval, the tumor recurrence rate, including evaluation of the number of recurrent tumors at two years post-treatment, progression of stage, progression of grade, occurrence of CIS, occurrence of distant metastases. In a submission by MEL in

2001, recurrence-free survival was indicated as the primary endpoint. In the MEL submission of January of this year, in preparation for this meeting, the primary endpoint was identified as time to recurrence.

Now, the inclusion criteria have also been discussed and I will not repeat these for you.

Looking at the demographics of the enrolled population, as noted, a total of 83 patients randomized, 41 and 42 respectively. There was a slight increase in the proportion of the patients of age 66 or greater in the control arm. Overall, for the first episode, 37 percent of patients presented in that fashion and 40 percent were stage Ta and the majority of patients were grade 2 or grade 3 in the enrollment.

Now, this slide indicates an overview of study results, and through the next several slides I will try to reconstruct as the sponsor has also presented the various analysis populations that have been considered. Of the total of 83 initially, 8 patients in total discontinued before the first time cystoscopy follow-up that was to take place. A total of seven of these were on the Synergo plus mitomycin C arm, one on the control arm. Subtracting these 8

patients, the applicant has identified a population considered valid for analysis or protocol consisting of 75 patients, 35 and 40. Just to note, in summary, 54 patients completed all therapy, that is the 8 induction and 4 maintenance treatments, 65 percent in total, somewhat evenly distributed.

Now, I want to spend a moment talking about the applicant's description of these early discontinuations, a total of eight patients, as we mentioned seven on the Synergo arm, one on the control arm. The first six, the applicant has identified as early withdraws or dropouts and the final two are described as protocol deviations. These were also patients in whom consent was withdrawn for the reasons indicated, and after the patients were withdrawn, they received mitomycin C alone. So keep this total of eight patients in mind. I have combined them for the subsequent slides.

Now, going back to the per-protocol or valid for analysis population as identified by the sponsor, the total of 83, and removing these 8 early discontinuations, the applicant provided us their information according to the Kaplan-Meier curves of the estimate of the two-year recurrence rates, and that is shown on this slide, 17.1, 61.6, with a log-

rank P value test of significance. And again, this analysis group includes the total of the eight patients who discontinued before first follow-up.

Now, you've heard also a description of additional analysis populations. This table attempts to summarize and present to you two additional analysis populations as described by the applicant. These analyses adjust both for randomization errors and add back that two protocol deviation patients but not the six early dropouts. So if we look at the total of 83 and remove the 6 early dropouts, discontinuations, you have 77 patients. And you get slightly different results for the analysis based -- because of this additional issue of the problem with randomization.

As you've heard, 5 pairs or 10 patients, 12 percent, had their randomization assignments switched, and apparently these 5 pairs symmetrically received the opposite treatment, and I think we don't completely understand just the mechanics of how this occurred, at least we haven't. The sponsor identified an evaluable group which they've called randomized intended. I think they merely mean analyzed on the basis of treatment that should have been given, and that gives you these two differences

in results for the two-year recurrence rate. And then the other group is randomized as treated, that is the analysis population is for patients evaluated based on the actual treatment as given in which the 10 patients were switched.

So putting these three populations together, this table indicates the applicant's estimated two-year recurrence rate for the two populations that adjust for the randomization errors and exclude the six early dropouts and the protocol population, the lower row here, shows the initial group I had defined for you minus eight patients. And again, the log-rank procedure was used for the analysis test, statistical test.

Now, this table adds one additional category. This is an attempt to get to an ITT population. All patients as they were assigned, that is as the treatment was intended to be, and this also uses a form of worst case censoring. The mechanism of censoring was not prespecified in the protocol. So with a total of 83 patients, and again using the applicant's calculation for their estimated 2 year recurrence rate, one has a 2 year recurrence rate of 38 percent on the Synergo arm versus 51 percent for the control arm of mitomycin C alone, and application

of the log-rank test does not yield a value less than .05.

In this worst case censoring analysis, as the sponsor did mention, the six dropouts were added back, and the assumption was made that one control patient was recurrence free and the five Synergo patients who had dropped out had disease recurrence, and that's why this is termed a worst case censoring application.

Now, this represents from the January 2008 applicant information. The analysis of a per-protocol group. This is not intention to treat. This is the 75 patient subgroups of the entire study. The lower curve is mitomycin C alone, the blue line here, and the number of patients on each arm are indicated here, and this is to capture the two-year experience.

This curve represents the data analysis if one used the intention to treat population combined with that description I gave you of worst case censoring. So all patients are added back and censoring convention applied as described here. The blue line represents again the mitomycin C control group. There's an early decline in the Synergo group due to the dropouts, the curves cross and then they

are roughly parallel but the mitomycin C line is lower.

Now, turning to secondary endpoints, the applicant has provided information. No stage progression was identified. No CIS subsequently developed, and a late follow-up of those patients available occurred, and no overall survival difference was identified between the two groups of patients. The applicant has reported to us a total of 14 deaths. No bladder cancer deaths. Five are described as due to tumors in other organs. We do not have pathology reports to review for that. There were three patients in this January summary to the FDA described to have metastases on the mitomycin C arm based on scans, but we have no pathology to examine here.

Now, this is the overall survival analysis submitted earlier. This is not the intention to treat population, but this is the -- and this is a shorter time interval than what you had seen earlier from the applicant. And one would not ordinarily expect to see a difference in overall survival due to the nature of this condition.

Turning to adverse events, there were more reported in total on the hyperthermia arm. We noted

that pain occurred in 40 percent of patients versus 0 percent on the control arm. There was more dysuria reported, and this bladder wall thermal reaction, which we'll talk a little bit more in a moment.

Pain on the Synergo therapy was reported in 17 of the 42 patients who received the hyperthermia. It was described as pain or intolerance to treatment in 10 of 42, and bladder spasms attributed to the catheter placement in another 7. And of this total 17 patients, 7 were rated as mild, 7 moderate and 3 were rated as severe. One Synergo patient, as well, developed a false urinary passage attributed to the larger size of the catheter that's necessary for this therapy.

The posterior wall thermal tissue reaction as mentioned related to the radio frequency antenna is visible by cystoscopy. The investigators described the condition as consisting of tissue necrosis in 23 of the 42 patients, 55 percent, and it was graded as mild, moderate or severe, in these numbers. A posterior wall ulcer was reported in 1 of the 42. Now, as described, none of these were determined to be transmural and no interventions were described as necessary to manage the condition.

Looking at another of the applicant's

studies for just a moment, the EPP, European Prophylactic Patient study, is an ongoing study of the commercial use in practice of this device. It is a single-arm study, and we are informed of 186 patients enrolled, 122 evaluated for efficacy. On this single-arm study, the estimated two-year recurrence rate is identified by the applicant as 32 percent. While we are reluctant to do cross-study comparisons, we did observe that in Study 102.1, the BCG alone control arm has a two-year recurrence rate of 32 percent.

Now, this is a study, commercial use in practice. With regard to the studies discussed here, Study 102.1 addresses a different question than 101.1 but the safety does appear to be similar. Approximately one-third of the patients are accrued at this time, and we do await the full study report. Study 101.1 is a prospective study of 83 patients, 42 of whom received the Synergo hyperthermia treatment for the proposed approval indication. The general treatment plan, the endpoints to your follow-up are reasonable choices for this disease. Adverse events are greater on the Synergo arm including all AEs, pain, dysuria, and this posterior bladder wall tissue reaction.

Now, in examining the study, the protocol, the information submitted and the amendments between 2001 and now with additional data, we do want to indicate what we term clinical limitations regarding the sponsor's pivotal study. At the time of randomization, on the randomization form, the patient's baseline characteristics were disclosed. The information was available. A misrandomization occurred. At one site, the BIMO auditor examined eight patients and four were misrandomized, and you've heard that a total of 5 pairs of patients have been identified in which the treatment assignments were switched, 10 of 83 or 12 percent of the population.

The original study protocol lacked a prespecified definition for the primary endpoint, or for an interim efficacy analysis performed after 64 patients had been enrolled, or the decision to stop at 83. Also a plan for analysis of the missing data and censoring conventions were lacking.

With respect to data collection in the study, case report forms to document study events were not introduced until three to four years after the study started. Two-thirds of the patients had been enrolled by that point. And while the source

records as audited by the BIMO examiner appeared to be transcribed accurately, there's no assurance that additional vital study information was not lost by the failure to document prospectively for all patients.

Pathology information regarding baseline and follow-up biopsy results was not prospectively and consistently captured in a structured format to assure accuracy and completeness of the information. For example, in the pathology reports available, baseline description regarding the presence of or involvement of the muscular layer of the bladder was inconsistently reported.

Also with respect to pathology, there was no central pathology review performed. And in the applicant's submission of January 2008, amendment 16, it states specifically no pathology report is available for 4 of 29 of the total reported recurrences.

Now, blinding has been commented on earlier, and patients and investigators knew their treatment plan. We agree, blinding of the treatment of itself was not practical. We do point out that no independent assessment or adjudication of the endpoint of tumor recurrence occurred in this study.

The dwell time in the bladder for the intravesical mitomycin C was not consistently recorded. Part of this issue had to do with the late availability of the case report forms. But treatment differences may have resulted from that variable, and we're not fully able to assess that.

For the Synergo patients, mitomycin C was removed by the catheter, whereas for the control patients, they were advised to void per schedule.

We also noted that the follow-up cystoscopy exams were not performed consistently at study sites. They may have been performed at local sites for patient convenience. We're not entirely clear of what information was captured or forwarded or how those study sites may have been instructed to perform the examinations.

Concomitant medications were not prospectively recorded and, therefore, concurrent use of other medications which may inform further regarding efficacy or safety is uncertain.

The potential for bias was not minimized in the applicant's pivotal study. A substantial asymmetry in early dropouts on the Synergo arm, seven versus 1, suggests additional adverse features of this therapy may be present. The strength of the

efficacy conclusions vary with the choice of the analysis population. Study 102.1 shares some of the similar concerns as we have identified in 101.1.

Now, of interest, the Study 101.1 was reported in the Journal of Clinical Oncology in 2003 by site investigators, and they described it as a multicentric study comparing intravesical chemotherapy alone with local hyperthermia for prophylaxis of recurrence at the three sites indicated and consisting of the 83 patients randomized. And the authors' conclusions in this published analysis was that, "These results were preliminary and need to be confirmed by larger, prospective, multicenter studies. The combined treatment was more cumbersome and requires a larger catheter. However, the reduction in the proportion of recurrences at 24 months in favor of thermo-chemotherapy encourages further clinical investigations."

Thank you.

DR. LI: Good morning, ladies and gentlemen, distinguished Panel members and guests. My name is Xuefeng Li, a Statistician in the Center for Devices and Radiological Health. I'm going to give you a brief overview of this PMA from the

statistical perspective.

This is the outline for my presentation. First, I will give you a brief introduction of the pivotal study design and the effectiveness results. Then I'll talk about the limitations of the pivotal study. After that, I will talk about other relevant data and studies for the Synergo device and their limitations. Finally, I will conclude with a summary.

The pivotal design Study 101.1 is a randomized, multicenter, unblinded study. Since previous speakers have talked about this design in great details, so I will not repeat them here. Note that the sponsor originally planned to enroll 150 patients. An intimate look was taken when 64 patients were enrolled and the study was stopped early when 83 patients have had had 2-year data.

This table gives a patient accountability and also lists the analysis populations. Since you have also heard it before, I will not repeat it here.

So this table summarizes effectiveness results for the primary effective endpoints based on different patient populations. In the all study patient population, missing patients were treated as failure in the Synergo group but success in the

control group. Except for this worst-case scenario, the Synergo group appears to have statistical lower two-year probability of recurrence than the control group. Note that those P-values are not adjusted for the interim look or the early stopping.

This table summarizes the results for all secondary endpoints.

Now, I would like to discuss some limitations associated with the pivotal trial. Actually, Dr. Kane has mentioned most of them as clinical limitations. Since they also have statistical impact, I will repeat them here briefly. First, this trial is an unblinded study. An independent, blinded review committee to adjudicate tumor related endpoints was not implemented in this study. Second, the sponsor listed six endpoints but did not clearly specify which ones are primarily and which ones are secondary in the protocol. Third, the primary hypothesis was not clearly stated, and the statement about the analysis method of the primary endpoint was not included in the protocol.

However, also primary endpoint and the corresponding hypothesis could be inferred from the weight of statement about the sample size, first, how missing data would be handled was not pre-specified

in the protocol. Finally, the interim analysis was severely lacking in detail. The adverse -- function, the -- of earlier stop for success and the sample size recalculation method were not stated in the protocol.

When considering these limitations together, it is very difficult to evaluate the potential bias introduced by them.

As you have seen, the sponsor also provided the long-term data and other relevant data and analysis for Synergo treatment.

So next I will briefly go through these analyses and discuss some limitations associated with them.

Here are the results of the long-term data of Study 101.1. Regarding the recurrence rate, the Synergo group has lower rates than control at both 5 years and 10 years. In terms of the overall survival, there are nine deaths in the control group and five deaths in the Synergo group until the year 2006. None of these deaths were due to the device.

It should be noted that the analyses of the long-term data were not pre-specified. The sponsor used the as-treated population and the missing data was not.

Here the descriptive data from Study 102.1, the sponsor expected to enroll 150 patients per arm. At the interim look, there are 51 Synergo patients and 53 control patients from Study 102.1, which are about 1/3 of the total patients expected to be enrolled. The 2-year recurrence rate for the Synergo group is 16.9 percent and for control group is 31.7 percent. No progression was observed at the interim look.

There are some limitations with the data from the Study 102.1. First, the data is from an unplanned interim look and the study is still ongoing. Second, the Study 102.1 and the Study 101.1 have different treatment regimen as previously discussed by Dr. Kane. Third, it is difficult to fully verify the patient comparability.

The sponsor also provided a combined analysis that pooled the data from Studies 101.1 and 102.1 together. The 2-year recurrence rate of the combined Synergo group is 17.1 percent based on the per protocol group.

Again, this combined analysis was not a planned analysis, and the patient comparability cannot be fully verified.

The sponsor also conducted the literature

review of control treatments in Studies 101.1 and 102.1. Based on meta-analysis, the sponsor reported a 2-year recurrence rate of 41.5 percent for the MMC treatment and 35.5 percent for the BCG treatment.

Again, this literature review is an unplanned analysis, and it is very difficult to verify the poolability across studies. In addition, the literature review is -- subject to publication bias. Here the publication bias means that positive results have a better chance of being published.

To summarize, the pivotal study appears to show that the Synergo treatment had a smaller two-year recurrence rate than that of the control. However, there are some limitations associated with this study as I have mentioned before. When these limitations are considered collectively, it potentially impairs the ability to interpret the statistical results and increase the uncertainty of the state of the conclusions. Other analyses provided by the sponsor appear to show supportive evidence of the safety and effectiveness of the Synergo device, but they all have their own limitations as mentioned before.

This ends my presentation. Thank you very much. Now, I turn the podium to Dr. Wei.

DR. WEI: Good morning, distinguished Panel members and members of audience. I'm Dr. Shaokui Wei. I'm an Epidemiologist in Division of Post-Market Surveillance, Office of Surveillance and Biometrics.

Today I will talk about post-approval study as have been proposed for the Synergo hyperthermia system submitted by Medical Enterprise. This presentation is based on the original protocol submitted to the FDA on January 4, 2008, that differ slightly from what the sponsor presented earlier.

Before we talk about the post-approval study, we need to clarify that the discussion of a post-approval study prior to a formal recommendation on the approvability of the PMA should not be interpreted to mean FDA is suggesting the Panel find the device approval. The plan to conduct the post-approval study does not decrease the threshold of evidence required to find the device approval. The pre-market data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of the safety and the effectiveness in order for the device to be found approvable.

This is the outline of my presentation. I

will start by describing the general principles and objectives of the post-approval studies. Here are the two general principles on the originals for the post-approval studies. The first one is to evaluate device performance and the potential device-related problems in the broader population over an extended period of time after pre-market establishment of reasonable device safety and effectiveness. Second, post-approval studies should not be used to evaluate unresolved issues from the pre-market phase that are important to the initial establishment of the reasonable assurance of the device safety and effectiveness.

These are the general objectives of the post-approval studies. The post-approval studies are conducted to gather post-market information on the longer-term performance. As we all know, pre-market clinical data are collected from patients that are highly selected and treated by the community-based physician. In contrast, the device be permitted to be on the market, patient that receive the device are less respected and the physicians who treated those patients are not limited to a physician that are participating in the pre-market study. Therefore, a post-approval study are also conducted to obtain the

data on (1) community performance; (2) effectiveness of training programs; (3) performance of the device in subgroups of the population. Additionally, some of the rare adverse events that were not observed in the pre-market may be present in the post-market phase as observation period attained and the patient population -- Therefore, post-approval study can be designed to monitor such adverse events.

Another reason for conducting post-approval studies to address its use and concern that the Panel members may -- based on their observation and experience.

Now, I will present the overview of the sponsor's proposal followed by assessment of the proposed study.

The Panel's proposal is to conduct a prospective, single-arm study to evaluate the safety of the device compared with the pre-market data 101.1. The main study endpoint will be the frequency of the anticipated adverse events, and the secondary endpoint will be any unanticipated adverse events. And, they plan to conduct null and alternative hypothesis test for each adverse event. They propose to include 211 patients in the intermediate and high-risk STCCB, including transurethral resection of

their tumor under the 12-month follow-up period with assessment every 3 months. They claim that the 211 subjects will allow for 80 percent of the power.

The next two slides I will present more detail about the primary endpoint and the study hypothesis.

As I mentioned earlier, the primary endpoint is frequency of anticipated adverse event. The adverse events are listed here, and they are posterior wall thermal reaction, urethral stenosis, hematuria, false route, hypotonic bladder, reduced bladder capacity, urinary tract infection and necrosis in other areas of the bladder.

And for each of adverse event risk, a null or alternative hypothesis will be conducted. The null and alternative hypotheses are formulated as follows: the null hypothesis is P greater than or equal to the pi plus delta; alternative hypothesis P less than pi plus delta. Where the pi represent the current rate of adverse event as established in the pivotal Study 101.1, and the delta is the largest acceptable difference between the study rate and the -- rate. The sponsor proposes the delta to be 10 percent for proportions over 50 percent and 5 percent when adverse event occurrence rate is small, for

example, a rare event. For each test -- will be claimed if the upper limit of 90 percent -- if less than the pi plus the delta.

Now, I would like to move onto the assessment of the sponsor's proposal. The first concern we have related to the basic study design, comparison group, the sponsor proposes to use a pre-market study group and a target control group. FDA believes this proposal is limited because, as I mentioned earlier, pre-market study of performance is highly selected patient population and are conducted in highly specialized center, and not represent or be comparable with post-market experience. And all the pre-market data came from outside U.S. We believe the most appropriate post-market comparator may be the existing of standard of care.

Next, I will present more pre-market data to make one more argument.

This table shows adverse events the sponsor plans to evaluate in the post-market study. Please note the pre-market safety profile of the device different by the study. Therefore, it is difficult to determine which pre-market study is the best comparator. Additionally, there are some frequent adverse events in the pre-market study that the

sponsor did not include in the original PSA proposal, such as pain which was observed in 41 percent in the Synergo patients in Study 101. There was no pain in the control Study 102. Fifty-three percent of the Synergo patient suffer with pain versus two percent in the control.

Starting -- with the study design, the study endpoint, the sponsor only considered the evaluation of the safety. There is no plan to assess post-market effectiveness. The long-term effectiveness in large and diverse patient population is still not clear.

Additionally, please note that although both 101 and 102 studies show Synergo has a reduced two-year recurrence rate, the deficiencies in these studies, addressed by Dr. Kane and Dr. Li in the previous FDA presentation, make the recurrence data difficult to interpret. There is also the question about the long-term survival. The pivotal Study 101 show that there was no significant difference in the overall survival rate between the two treatment groups. There was a total of 14 deaths, 9 in the control group, 5 in the Synergo, reported since the start of the clinical study in 1999 until later in 2006. None of the deaths were known to be due to

STCCB.

The third limitation of study design is the length of follow-up. Current proposal only considers one year of follow-up. Since STCCB has a long waiting period, slow progression, most cancer recurrence may not occur in the one-year follow-up and some adverse event, such as urethral stricture develop slowly and appear after one year of -- So one year of follow-up may not be sufficient to assess long-term performance of this device.

Our first concern relates to the statistical analysis plan. They plan to conduct a hypothesis test for each anticipated adverse events. There's a 10 percent delta for the adverse event with 50 percent frequency and a delta of 5 percent for the rare adverse event. The definitions of a common versus a rare event are not clear. The rationale for the selection of dealt is not presented.

Specifically, here are chosen delta for each adverse event. Those at the present are less than 10 percent of frequency in the pre-market Study 101. If you compare with the post-market rate there was a 5 percent delta. The posterior wall reaction if you compare is a 10 percent delta.

Now, I will present the issues that we

would like the Panel members to consider this afternoon when addressing the Panel questions.

First, we would like to hear your comments on the comparison group. As mentioned earlier, the sponsor's proposal to use a pre-market study group as a historic control group. Please discuss what is the most appropriate comparison group for the post-approval study? We believe the pre-market group is not appropriate as a comparison group for the post-approval study and the -- of the more appropriate comparison group may be the standard of care.

Second, we would like to hear your comment on the study endpoint. The proposed study only includes the evaluation of the device safety but it does not include a plan to assess the post-market effectiveness. Should the effectiveness be studied post-market? If so, what endpoint should be studied? Should it be the recurrence rate, patient survival or both?

And thirdly, the current proposal consider only one-year follow-up. We would like you to discuss whether one year of follow is sufficient to assess the long-term performance of this device. Please consider that STCCB has a long waiting period and a slow progression, and the some of the adverse

events develop slowly.

Finally, please discuss and make recommendations on the definition for rare versus common adverse events and the rationale for the chosen deltas.

This concludes my presentation. The floor is now open to the questions for the FDA. Thank you.

DR. TALAMINI: I'd like to thank the FDA speakers for their presentations and open up the Panel to questions specifically for the FDA. We have 15 minutes scheduled prior to lunch for that, and we're just about on time. So I'd ask Panel members, if you have questions specifically to the FDA regarding their presentations. Dr. Connor, perhaps I would invite you specifically since there's so much statistical --

DR. CONNOR: (Off mic.)

DR. TALAMINI: In the meantime, Dr. Donatucci?

DR. DONATUCCI: Yeah. While you're reviewing your notes, I just have a question for Dr. Kane. You presented a slide I believe and I've been looking for it and haven't found it, about progression, differences between BCG and mitomycin C. If I recall, there was an eight percent and four

percent --

DR. KANE: That was Dr. Herrera.

DR. DONATUCCI: Who was that? I'm sorry.

DR. KANE: Dr. Herrera.

DR. DONATUCCI: Dr. Herrera, okay. Maybe that's why I can't find it. Thank you.

DR. CONNOR: So I guess my first question, maybe this is the question of the day, so it's good to get FDA's opinion. I'm not used to having to have the microphone this close. One of the questions that's continually put out are are there biases in this study, and we recognize, you know, that the study design and implementation was not ideal. You know, we don't know the consequences, the biases of this study. Do those in FDA who have thought long and hard about the consequences of these biases have an opinion, and let me know if this is a question I can ask, if those biases are enough to overcome what looks like to be an effective treatment? I mean, is the concern that biases are so huge that it doesn't look like this is as effective as at least in the efficacy data looks like the treatment is?

MS. BROGDON: I'd like to respond to that.

DR. CONNOR: Okay.

MS. BROGDON: This is one of the issues

that we really wanted the Panel's input on. I think it wouldn't be appropriate for us to give an opinion.

DR. CONNOR: Okay.

DR. TALAMINI: Perhaps I could ask a very practical question, and I couldn't quite tell, and this is to FDA specifically. It sounds as if the sponsors have expressed a change in their plans for a post-market study. Was the FDA aware of that? And, has the FDA taken that into consideration in this current presentation?

DR. BAXLEY: The post-approval study that we presented was sent to us as part of our PMA review in 2007, and that was the only one submitted officially to the PMA. I think recently they've had some change in what they would like to propose, and that was not formally reviewed by us. That came in the Panel package that was sent to you all. So we've looked at it but we haven't formally reviewed it.

DR. TALAMINI: Thank you.

DR. BAXLEY: We weren't able to present anything else.

DR. TALAMINI: Other questions for the FDA? Dr. Connor. Okay. Let's go around this way. Dr. Redman.

DR. REDMAN: I have several but I want a

clarification that we can ask them questions later on after --

DR. TALAMINI: We indeed can ask questions later on.

DR. REDMAN: One questions involves slide 60, including all the patients with a signed and tended to treat. Has anybody done the numbers with just dropping out the three patients that never received any treatment which probably reflects the consent process and not the treatment effect in the worst-case scenario, and if those three patients are dropped, is the worst-case scenario those that included patients who received any treatment though may have stopped treatment prematurely, does that treatment effect still hold? Should I go through them or --

DR. TALAMINI: Why don't you go through them and then we'll allow the FDA to figure which ones they can answer quickly and which might require more analysis for later today.

DR. REDMAN: Slide 70 looked at possible data being supplied to the randomization. I'm assuming this was not a stratified randomization. Pre-study stratified by grade or Ta, T1, in that regard. Okay. However, even if that didn't occur,

my memory is that there was no major difference in the major prognostic factors. It still held up. So even though it wasn't stratified for that, it's unfortunate, but there was still no difference in that?

MS. BROGDON: Excuse me. I think it would be good if we could get the sponsor's responses on the record rather than having nodding of heads or shaking of heads.

DR. TALAMINI: So would you prefer that the sponsors -- that we broaden this set of questioning now to beyond just the FDA or have that occur later on?

MS. BROGDON: I think it's up to you.

DR. TALAMINI: Perhaps we could have an acknowledgment from the sponsor in response to those questions.

DR. O'DONNELL: Can you repeat the question?

DR. REDMAN: No pre-study stratification.

DR. O'DONNELL: Correct. No pre-study stratification.

DR. REDMAN: But your data showed that the major prognostic factors, there were no differences between the groups, if my memory's right.

DR. O'DONNELL: Right. They were evenly balanced, and there was no difference in the prognosis facts between the two groups.

DR. REDMAN: This is nexus to the FDA. On slide 72, just clarify for me, you've seen the CRFs and you're comfortable with the CRFs but there was a comment made that even though there was retrospective data collected on those CRFs, that there was a fear that some additional vital study information could not be lost in that process. What was the potential vital study information that you were concerned about?

DR. KANE: I think if we knew it, we would not be concerned about it. Our observation was simply that we were unsure what may not have been captured, written into a hospital record, that may have occurred and I guess corollary to that is the fact that some of the follow-up cystoscopies were not performed at the study sites, and we're looking at a great deal of reconstructed information.

DR. REDMAN: I accept that, but the second point you made about the cystoscopies not being done at the study site, were those cystoscopies during the first two years of follow-up that were protocol specific that were done --

DR. KANE: Yes.

DR. REDMAN: -- outside --

DR. KANE: Yes.

DR. REDMAN: -- and do you know the number of those for each arm that were performed not at the study site?

DR. KANE: No, I don't. No, I don't. Just the comment that that --

DR. REDMAN: Just the comment that it occurred.

DR. KANE: That is occurred.

DR. REDMAN: Okay. And the original biopsy material, and I guess this would go to the sponsor, too, my concern is that even though some of the ones that did not have muscle on the biopsy material, were there also blind biopsies done to confirm that there was no CIS and was that equal between groups and again that I don't expect you to be able to answer at this point in time, but it would be interesting to know.

DR. TALAMINI: I think the sponsor has a response at least to one of those specifics regarding the studies. So we'll let them respond.

MS. STEIN: I just wanted to comment the issue that Dr. Kane mentioned regarding the

cystoscopies were not performed at the site. I'm not sure exactly where he got that information from because all cystoscopies were performed only at the sites by the PIs, by the principal investigators and recorded both in the hospital source documentation and on the CRFs. Okay. I just wanted to clarify that.

DR. TALAMINI: Thank you. Dr. Redman, additional? Dr. Dahm?

DR. DAHM: One of the gentlemen that gave the statistics presentation, I would ask to comment on what I found as a footnote to slide 86 where it talks about not adjusted for interim look or early stopping. I guess you're suggesting that the fact that the study was stopped early for benefit may be a potential source of bias. I think that relates to recent studies in the methodology literature, that that's just something that we should look for, too. Is this something you can comment on?

DR. LI: We know that if we do an interim analysis, that -- rate would be inflated. So it would not be under 5 percent, might be like 10 percent, something like that. So we have to pre-specify -- function to control the overall -- rate once we have interim analysis that we could study for

early claim of success. So the sponsor did pre-specify a method for doing that. So we're not sure whether -- rate is controlled or not. Actually, I have a backup slide.

DR. DAHM: Do I understand correctly that this would exaggerate the observed treatment effect, that that would be the direction of the bias if you stopped the trial early for benefit which is common by the way, which is very common in these kind of studies? But is that the concern?

DR. LI: Yes. So here these slides lists two, why we used the method for control of -- rate when the trial has an interim look. The first one is O'Brian-Fleming -- rate. If we take a look at we have 64 patients out of the 150 patients are randomly expected, so the P-value should be under .0013 in order to claim study success at this interim look. The second method is called Pocock boundary. So, for example, if we take an interim look, and we have 64 patients. So the P-value should be under .0277 in order to claim early success.

So the sponsor P-value, as-treated populations, is well below this O'Brian-Fleming boundary. So it's still statistically significant but for as intended population, the P-values are

above this O'Brian-Fleming boundary. So when --

DR. DAHM: Can you repeat your last sentence again?

DR. LI: If we use the first method, the sponsor's analysis based on as intended populations will not be statistically significant. That means the sponsor P-value, if we check the slides, my slides 85 or 86, actually 86, we see that -- excuse me. Look at the P-values. These two P-values are above .0013, the threshold from the O'Brian-Fleming boundary. So the first two analysis populations would give statistical insignificant results. For the last two, as-treated populations, we still have statistical significant.

DR. CONNOR: Can I speak to something Dr. Dahm asked?

DR. TALAMINI: Yeah, from the Panel's point of view, we're still supposed to be asking questions.

DR. CONNOR: I think it's a brief clarifying thing maybe. Your question was whether the interim analysis would bias the treatment effect estimate. So the answer is the treatment effect we observe is not biased by looking early. The probability of them making a type one error, the probability of them, you know, saying the effect,

that is inflated, but the size of the effect we estimate is not inflated by this. And that's about all we can talk about.

DR. TALAMINI: So I want to make sure that we keep to asking the FDA questions regarding their presentations as much as we can while still being fair to the sponsors to allow them to respond. So other -- does that get to your question?

DR. DAHM: Yes, it does. Thank you.

DR. DONATUCCI: Can I? I'm confused now. I wasn't confused going in. Now, I'm really confused. You know, I haven't had statistics since college but my understanding of a P-value was that either you prove the known hypotheses or you don't. So it's either by chance or not by -- it's just a percentage of probability that this is a chance observance rather than a treatment effect. I've never seen before anybody say specifically -- this boundary thing is completely new to me. So you're saying that, and I used to dismiss anything less than .01 as meaningless, the difference of being meaningless, but you're now telling me that you need to see, in order for that treatment effect to be real and not just by chance, in an interim analysis you need to see like Pocock's hypothesis, three

statistically -- three significant figures? You know, so less than .01 is meaningless to me now. It -- I'm lost. Help me here.

DR. LI: Yes. My idea is that you frequently check the data. By chance you may observe success earlier but this will inflate the -- rate. That means actually there's no treatment effect but you claim there is a treatment effect if you still use .05 to control the -- rate. So we have to --

DR. DONATUCCI: Lower the P-value.

DR. LI: -- lower the P-value, lower the bar.

DR. DONATUCCI: That's pretty low. That's the first time I heard of that. Thank you.

DR. TALAMINI: So, Dr. Connor, perhaps you'd be willing to -- as I understand it, as a layman, this is the statistical bar that you need to say that you can stop the study early or evaluate midway through. Is that correct?

DR. CONNOR: Right. You can imagine a situation where every time a patient comes in, we look at the data again, and so we would be looking at the data 150 times in a 150 patient trial. If ever that P-value got below .05, the sponsor goes, we win. Obviously the type one error rate is much higher than

.05 in that. So I think that example may make sense. So these values are a way to quote spend, your 5 percent error. The sponsor says we have, you know, or the agreement between FDA and the sponsor says we have 5 percent error rate. We're willing to make an error rate of, you know, 1 percent early on and then have a 4 percent error rate later. So it's a way to spread out that 5 percent chance of saying something is effective when it actually isn't.

DR. TALAMINI: So on this particular question, does the sponsor have a comment or response? Yes. Yes, sir.

DR. MARCOVICH: Just a couple of minor comments. First of all, at the time of this, this was called by the Data Safety Monitoring Board, and they weren't aware of the randomization or it was discovered much later. The second thing is that the overall recurrence rates in the 101 study is essentially identical to the 102 study. So this does not appear to be just a fluke. Those curves are, you know, right on, and the mitomycin recurrence rates are right on with the expectation of the literature. So there doesn't appear to be anything unusual in the results in the 101 study.

DR. TALAMINI: Thank you. Are there

questions about the FDA presentation from the Panel? Yes, sir.

DR. BHUTANI: I have questions for the FDA. I refer to slide 13 which is on the chronology. In 2001, the PMA was submitted to the FDA. What feedback was provided to the sponsor regarding the study design or problems, if any, or about statistical concerns and then I want to know what the in-depth review cycles are from 2001 to 2004. I presume they are with the FDA reviewing the data, and then lastly in 2005, when FDA conducted bioresearch monitoring inspections, and found the CRFs, retrospectively collected CRFs to be acceptable, was any feedback provided to the sponsor about potential problems of vital information being missed that could become an issue if the device is brought for a PMA to the FDA in the future? Thank you.

DR. BAXLEY: Let me start with the in-depth review cycles. Those were times when the ball was in FDA's court for our review, and the first review cycle was with review of the original PMA. The next two were with review of additional information we received, that we requested, and they were mainly with how the study was conducted and what the results are and additional information on case report forms

and pathology reports, detailed information. The bioresearch monitoring inspection was just to audit the data and to see if it's factual and it was. But the concern raised here is a review concern just on how the study's conducted, not an audit issue.

DR. TALAMINI: Yes, sir. Dr. Layton.

DR. LAYTON: I have a couple of questions relative to some of the earlier slides. One of them was the preclinical review and during the preclinical review you said that you had no concerns with the device other than the shelf life. Has that been taken care of? And the preclinical review that you did do relative to that, is there any comments relative to the failure modes or the adverse events?

DR. BAXLEY: Our first several review cycles were also heavily involved with the preclinical review, and additional information was provided in those two cycles that adequately addressed, you know, the concerns we had. So we're looking at that in depth during the early phase. And there was hazard analysis information in there that looked at failure modes and reliability and that's since been resolved.

DR. LAYTON: All right. The other question that I have was relative to, and I think this is what

I heard, during the clinical data sources slide, you made a comment, I thought, of unplanned studies, and I didn't know what you meant by that.

DR. BAXLEY: I think I used unplanned interim analysis of studies.

DR. LAYTON: Okay. All right. Thank you.

DR. BAXLEY: But not unplanned studies.

DR. LAYTON: All right. Thank you.

DR. TALAMINI: Seeing no other questions, I think there's at least one or two questions still on the table. Dr. Redman had the question about the worst-case scenario re-analysis that I hope the FDA group can address or can answer for us later on. I think that's the only one that's still on the table. Is that correct?

Okay. So given that, we will plan to break for lunch. I remind the Panel members that there should be no discussion of the PMA during the break amongst themselves, with the sponsor or with the public. We will reconvene again in this room at 1:00 p.m. Please take any personal belongings you may want with you at this time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene. Thank you. See you at 1:00.

(Whereupon, at 12:00 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:05 p.m.)

DR. TALAMINI: I'd like to call the Panel back to order, it being it looks like about 1:05. And I'd like to take up, if we could with the questions still on the table just prior to lunch that Dr. Redman asked the FDA to clarify, and I think we do have a response. Is that correct?

DR. BAXLEY: Yeah. The information that was asked about in that question, FDA didn't have presented to us. In the meantime, the firm has provided that information and a copy has been handed out to the Panel of a Kaplan-Meier curve. If you have any questions, I would refer to the company.

DR. TALAMINI: Okay. With that being said, I would ask the company to come forward to address any detailed issues raised in the morning session that the company has been asked to address after the lunch break and perhaps also this new data analysis. So sponsors?

MS. DEUTSCH: Okay. I will just quickly go through the re-analysis that we provided.

DR. TALAMINI: Can everybody hear her?

UNIDENTIFIED SPEAKER: No.

MS. DEUTSCH: Sorry. What we were

requested to do was provide an analysis of the worst-case scenario excluding three patients from the analysis and this is what we have in the Kaplan-Meier curve that you have in front of you. The total number of patients instead of 83 is 80. Estimated from the Kaplan-Meier curves, you can see that there's a 25.6 recurrence rate in the Synergo group and nearly 60 percent in the mitomycin group, the -- test. We still have a significant at P equals 0.037.

DR. TALAMINI: Thank you. Other responses from the sponsors?

DR. GROSSMAN: I think we've addressed most of the major concerns that we were asked this morning. A couple of minor points. The number of adverse events recorded prior to '97 and after '97 were very similar, suggesting that the doubts, the review of the case before us, retrospective case report forms was not a problem. The overall presentation of the data of the 101 and 102 studies again show consistency in the data, the overall experience with mitomycin and BCG are very similar. This is in general a very high-risk group. Half the patients were high-risk overall. So this puts the treated population at very high risk for recurrence, and I think the data stands for themselves. We, of

course, would be happy to address any other concerns that you have.

DR. TALAMINI: Thank you very much.

So now the Panel enters into a phase of public discussion, both questions and discussion which eventually will funnel down to answering the specific sets of questions that the Panel has before them for consideration but before getting to those specific questions, we'd like to entertain any other more general discussion or questions that would open up such discussion from the panel. So I'll open it up to any Panel member. Yes, ma'am.

MS. STOKES: I have a question of FDA. The introduction of the lit review of controls, what significance does that play? The slide number is 96.

DR. TALAMINI: Perhaps you could repeat the question for us.

MS. STOKES: Slide number 96 refers to lit review of controls, and my question is what is the significance of introducing lit review, and is it a necessary support of evidence?

DR. LI: So can you repeat the question again? I'm sorry.

MS. STOKES: If you look at slide 96, you've introduced the lit review of the controls, and

my question is, what is the significant of that information?

DR. LI: Well, the sponsor wanted to show that data they observed in Study 101.1 and 102.1, only for control arms, they're consistent with those studies in the literature. That's their purpose, to show this literature review. So I'm a statistician. I don't know how to evaluate this particular information. So I just wanted to point out that there are some limitations with the literature review from a statistical perspective.

MS. STOKES: Okay. Thank you.

DR. LI: You're welcome.

DR. TALAMINI: Other questions from the Panel? Dr. Connor.

DR. CONNOR: So this is a question regarding the choice of control group and precisely what was done in the control group. So I notice that the MMC in the first study, 101.1, the MMC was preheated in the treatment group but not administered at room temperature in the control group. Presumably increasing the temperature of the bladder contributes to the efficacy benefit we see. I wondered if there's any information whatsoever on what the treatment effect would be just from preheating the

MMC but not using your device. Or why for instance or why perhaps that in the control group, the drug wasn't preheated similar to like it was in the treatment group?

DR. TALAMINI: So this is a question for the sponsor?

DR. CONNOR: Yes.

DR. O'DONNELL: So the traditional way we give intravesical chemotherapy is we either make it up in our clinic or we have our pharmacy group prepare it and send it down to us. It comes at room temperature and we give it. So that's basically the standard of how we do it. You can imagine that the bladder, as any body cavity, is a huge heat sink. If you put something in it, it will quickly equilibrate to the body temperature, whereas it may take a few minutes to make that equilibration. I'm not aware that anyone has been able to show, in fact, there were earlier attempts to preheat liquids and put them in the bladder and nothing ever came of that from a clinical standpoint, and it probably is due to the fact that simply, you know, small volumes in a big cavity, boom, it's going to equilibrate rather quickly and not make any difference.

DR. CONNOR: Can I follow that along then

and ask why then you did preheat MMC for patients in the treatment group?

DR. GROSSMAN: That was done to prevent a significant altered sensation because the bladder was being heated by the microwave, and we didn't want to put in cold mitomycin to increase the rate of bladder spasms. So we were trying to get the mitomycin up to temperature to the bladder and then, in fact, during the treatment, the mitomycin is extracted and cooled and circulated so it doesn't overheat but it was just done initially to equalize things and minimize thermal shock.

DR. CONNOR: Okay. Thank you.

DR. TALAMINI: So I have two questions which will sound naïve, but I think they're probably important for the public record. The first is what is the evidence that this is not simply giving systemic doses of mitomycin C and that that is the effect that we're seeing here, and the microwave and so forth is simply an epi phenomenon. That's question number 1.

Question number 2, if you could speak to the discrepancy between the survival data and the recurrence data, and what you might predict, and it's not fair to predict, but what you might predict could

be the survival effect of this treatment in the long run.

DR. O'DONNELL: Okay. I'll speak first to the idea of a systemic administration of chemotherapy. One of the things we've learned from at least the clinical experience is that chemotherapy when it is given appropriately for advanced bladder cancer, which includes disease still in existence in the bladder, is reasonably good at dealing with deeply invasive disease but actually is relatively poor at dealing with surface disease such as carcinoma in situ and papillary disease. The same can be said with radiation, and it may very well be the case that the blood supply to the areas closest to the mucosa that basically incorporates with the urine is a source of concentration gradient and so you lose that effect. So we don't really -- even when the case is when it's given for another reason, we don't really see an effect on superficial disease.

The second point is that there is actually another device-related treatment for enhancing mitomycin C administration. Actually, there have been two parallel kinds of studies. One was an attempt, in the U.S., to increase the dosage and give it better concentration gradient and with that, you

saw a corresponding increase in serum levels and improvement in mitomycin effect. So there seems to be a relationship between the ability to give a better concentration gradient, dissolution of the tissue and tissue levels were measured in that one and, in fact, to give it a clinical effect.

The same thing was seen from an electromotive therapy, use -- pheresis to try drive things through. Again, the same epi phenomenon of -- well, I shouldn't say epi phenomenon. The same phenomenon of an increased serum level translating into an increased tissue level translating into a beneficial clinical effect. So these in aggregate would suggest that what you're getting is a tissue penetration effect, a better tissue penetration with a hyperthermia and the medication, rather not with one or the other by itself. The levels of mitomycin that are going in are nowhere near even those absorbed, the level that you would consider for systemic does given for other reasons like indication of pancreatic cancer or something like that.

And the second point was about survival. One thing to understand about the recurrence and survival rates of bladder cancer is that -- I showed you that recurrence curve which is an exponential

decay. The progression rate on the other hand is more of a linear phenomenon, and it's an order of magnitude different. And so in order to see any differences in survival on progression over time, you need large studies, highly risk event prone patients and it's extremely rare to see any data for progression and survival data in the literature. The only results that have really come out have been in large med analysis with 2500 patients, that have been able to see a small difference for BCG progression.

DR. TALAMINI: So then in follow-up, to ask it a slightly different way, there are certainly diseases where preventing recurrences does not help long-term survival and is therefore just torturing the patient in the interim. So what is the evidence in bladder cancer to the contrary?

DR. O'DONNELL: You have to ask yourself is there a benefit in preventing the patient from coming in multiple times to have a procedure under anesthesia, enduring the psychological harm of knowing they have cancer or cancer has recurred, and then you have the suggestion of maybe there is a benefit but we don't -- you saw even a difference in this group but the numbers were too small to save any statistical matters on it. So that will probably

remain an unanswered question but the other benefits of preventing the necessary treatments, the anesthesia, enduring the psychological aspects of having cancer, having to go in for recurrences and living under that umbrella, still remain.

DR. TALAMINI: Dr. Donatucci.

DR. DONATUCCI: To follow-up on what you just said because for me, I mean discussion really has to do with survival, and my knowledge of bladder cancer is limited, despite the fact I'm a urologist, because that's not what I do, but my memory is that patients with invasive disease generally tend to show up with it when they present. Patients with superficial disease usually remain superficial, and the hard part is trying to determine ahead of time which of the very few people are going to go from superficial to invasive disease. Now, we do know that patients with CIS and T1 disease high grade are the group that are likely to progress, and just to follow your thought one step further and take it back to the public representative who spoke earlier, that's the group that may actually have prophylactic cystectomy and that is -- we talk about adverse events and what the adverse event comparative issues are, but one adverse event we don't talk about is

taking a patient who's given a prophylactic cystectomy because of their high-risk of progression to muscle invasive disease, and there's not that many of them, but that is clearly a group of patients who would benefit.

But I do agree with what you were saying earlier that for most patients with superficial disease, the fact that you reduce recurrences does not translate into any appreciable diminution of risk of progression. And so we are talking about essentially what Dr. O'Donnell says, reducing the number of returns for cystoscopies and TURs, et cetera, et cetera, and it's a -- we're not talking survival. We're talking about just in psychologic and local symptomatology and then you have to say exactly whether the cure is worse than the risk of leaving them uncured.

DR. TALAMINI: Does the sponsor have a response?

DR. GROSSMAN: Yeah. I'd like to address the issue because it's really very, very critical. BCG, of course, is approved for recurrence. In the large Southwest Oncology Group trial, BCG maintenance versus no maintenance, there was a large significant difference in recurrence rate. There was a smaller

but still significant difference as with maintenance compared to no maintenance, in the rate of, I forget exactly the term, but the requirement to switch therapy to something else which was reasonably aggressive, largely cystectomy. So there were fewer rates of significant treatment failures with the maintenance arm, and there was even a trend. I think the P-value was .08 for survival which is really very impressive because the study was a modest size. All patients came in with non-muscle invasive disease and many of these deaths were actually from other causes, not all from bladder cancer.

So the odds are stacked against you for showing improvement in survival. So is preventing a recurrence good? Yes. Bladder cancer is the most expensive cancer to treat overall, and most of the costs are actually driven by recurrent disease and transurethral resections and repeated hospitalizations. This is an older population, and every time you go to the operating room and get an anesthetic, it's not good for you. There are small but there are real risks associated with transurethral resections. So preventing recurrence is a good thing. Prevent recurrence is a sure way of preventing progression, and if you had a large enough

study I think you would almost certainly show that aggressive intravesical treatment compared to transurethral resection alone is going to decrease recurrence, decrease progression, decrease survival. It hasn't been done just because the numbers are very small. They're stacked against you, and nobody has had large enough studies and especially with long enough follow-up to reliably answer that question.

DR. DONATUCCI: May I ask Dr. Kane to respond because slide 39 you presented data that said with superficial transitional cell carcinoma of the bladder, it's a heterogeneous population, outcomes vary, recurrence is common, progression is less common and not altered by therapy. So that's in direct contradiction to what you just said about preventing recurrence, prevent progression.

DR. O'DONNELL: Would you like me to answer that? I'm sorry, or address that.

DR. DONATUCCI: Somebody.

DR. O'DONNELL: So progression survival are the hardest terms to come to grip with because of the small event rate over time. As I mentioned, you need large studies, high-risk patients, for long periods of time.

Just to give you an example of how the

field is evolving, when the first guidelines came out in 1999 from the AUA and the 2002 guidelines from the EAU, progression was not even on the table because there essentially was not data. The data really came out just about two or three years ago with large meta analyses, mostly from the European ERTC Group which looked at -- there were two other meta analyses that backed it up, that looked at all accumulated data with BCG and discovered, for instance, that in studies that had BCG plus at least a year of maintenance, there was a real difference. It was a relative difference in progression, reduction by 27 percent.

DR. DONATUCCI: All right. But what's the absolute number? Twenty-seven percent.

DR. O'DONNELL: It went from 13 percent to 9 percent. It was small amounts.

DR. DONATUCCI: Right, but I mean that could be two patients.

DR. O'DONNELL: It depends on your sample size obviously.

DR. DONATUCCI: Right.

DR. O'DONNELL: So the point is that you can see a difference with aggressive therapy. To ask any study to demonstrate that requires you to make an

enormous investment in healthcare resources to ask that question.

DR. DONATUCCI: So what you're saying, if I understand it, is that frankly while this may occur, if it takes that many patients, it's not that big of problem.

DR. O'DONNELL: It's a --

DR. DONATUCCI: Not an individual perspective but from a healthcare perspective.

DR. O'DONNELL: Relatively speaking, it's a small percentage of patients.

DR. DONATUCCI: Relatively speaking, it's a small number of patients that progress from superficial to invasive disease.

DR. O'DONNELL: About 20 percent of those patients that present superficial disease that enter into the muscle invasive pool of patients, yes.

DR. TALAMINI: So having raised the question, let me rein the question in a little bit. In this device, we're looking at recurrence and not overall survival. So it was a little bit of an unfair question to ask but for me I thought it was important to put within the framework of the overall disease and how people do.

DR. O'DONNELL: Certainly.

DR. TALAMINI: Yes, sir.

DR. WITJES: Maybe I could just add some of the figures because I was co-author on that -- and the -- analysis was 4500 patients and we had a difference in progression of 12 versus 9 percent, 11.8 percent. So indeed it's a limited number of patients that have progression and the relative reduction is around 25 percent.

DR. TALAMINI: Other questions for the Panel? Dr. Dahm?

DR. DAHM: I have two questions. One relates to understanding the device better. There's a rendering -- artistic rendering of the device, slide 24 of the sponsor's presentation that suggests that the catheter is kind of in a central position in the bladder but I would suspect, unless there's a specific mechanism to put it there, it actually in many patients will be lying on the posterior wall of the bladder and that would explain some of the side effects. Is that a correct understanding? So to a certain extent this picture may be misleading just with that regard.

DR. WITJES: Well, the misleading part is that the tip of the catheter is not as large as it's suggested here.

DR. DAHM: Yeah.

DR. WITJES: You put the catheter in and you empty the bladder. You pull the catheter out of the bladder so that you sort of position the catheter at the point you'd like --

DR. DAHM: Do you put traction on the catheter?

DR. WITJES: We don't put traction on, but it's quite a heavy catheter. So it's positioned at the bladder neck, and then obviously what you'll say is the tip of the catheter is close to the posterior wall. Now, you have some additional -- that's a mechanical irritation of the mucosa and of course, the radio frequency antenna is closest to that part. That explains the posterior wall --

DR. DAHM: Okay.

DR. WITJES: -- thermal reaction, absolutely.

DR. DAHM: Okay. The second question, we're asked to look at 101 as the pivotal study, and I took from Dr. O'Donnell's presentation as well as from Dr. Grossman's presentation that most people that we're targeting this device for with intermediate and high grade bladder cancer would be -- in this country would be getting BCG rather

than mitomycin C. And I notice that in your second study, that is your control. Would BCG not be a better control, a more appropriate control to look at the effectiveness of this, of this device?

DR. WITJES: Well, if you refer to Study 101, yes, we realize that this study was thought of in the beginning of the nineties, when BCG was actually just at the table. The initial BCG studies are from that period.

DR. DAHM: Okay.

DR. WITJES: And I think the choice in those days when also mitomycin C was still advised for even progression in the EAU, AUA guidelines in 1999. So I think as to the choice in those has been Synergo versus mitomycin C, and obviously when we spoke about the new trial in the beginning of this century, which was for BCG, so that's I think the development of the knowledge of how you treat bladder cancer.

DR. TALAMINI: Dr. Lippert.

DR. LIPPERT: I also wanted to ask about the posterior part because in that same diagram I see little prongs coming out interiorally, laterally and posteriorally. Is it -- so it's not really true that it's really lying on the posterior bladder wall that

you have more of a tissue effect on the bladder wall? I mean does it make sense that the whole bladder is heated equally?

DR. WITJES: Well, we have five thermocouples. Two are in the urethra and three, they're very floppy things. So they just press against the bladder wall. They don't damage that at all --

DR. LIPPERT: But they tend to go posteriorally?

DR. WITJES: The thermal antennas? No, they are from side, left side and right side. So they are let's say more or less in different spaces in the bladder. That's not only on the backside. Obviously we don't measure the temperature in the whole bladder. You have sort of an average of the five thermocouples you have, and indeed there are maybe at the spot, which is closest to the radio frequency wire, that you might have a little bit higher temperature.

DR. LIPPERT: So the posterior radio frequency wire is posterior?

DR. WITJES: Yeah, because the patients are attached to the device and they're laying down which --

DR. LIPPERT: So because they're supined, the wire, it falls down to the posterior bladder wall?

DR. WITJES: More or less, yeah, but that's not the intended. It's just so light that it is not due to gravity going -- it's not that all the thermocouples are in the back of the bladder. They are spread through the bladder.

DR. LIPPERT: Right.

DR. O'DONNELL: If I may, just a point of clarification. The microwave energy doesn't come from the thermocouples at all.

DR. LIPPERT: Right.

DR. O'DONNELL: They are temperature probes only. So the antenna is in the middle part of the catheter itself. So those aren't -- that is fixed by the catheter position which may by gravity or by position tend to go towards the posterior wall.

DR. LIPPERT: That's what I -- okay. And then the question he asked about the -- well, the literature review, you looked at BCG for comparison and you looked at mitomycin C, but you didn't look at any comparisons with BCG with Interferon.

DR. O'DONNELL: I've done a lot of work with BCG with Interferon and to date there has only

been one BCG+Interferon versus BCG randomized trial. We actually just presented it at this year's AUA, and we don't have the details of that. We haven't even sorted it out yet. I would just tell you that the result of that presentation was that there was no different BCG and BCG with Interferon for first time patients. So at the moment, we don't see that BCG with Interferon is a different or superior control versus BCG for another new therapy. That's all we can say at this point, even though for recurrences, BCG failures, we at least have the phase two data that we see reasonably good effects of BCG+Interferon.

DR. LIPPERT: But you're saying that would be a different patient group than this that we're looking at, intermediate and high-risk, because you said those are first time.

DR. O'DONNELL: Okay. So not really a different patient group in terms of the intermediate high-risk groups by the EAU criteria but those patients that we've at least focused most of the data on for BCG with Interferon, are patients that have failed BCG at least once, whereas the application here for the Synergo group is even for up front patients with intermediate and high-risk group as

even a first time treatment. And it does represent, you know, a new therapy option for the high-risk patients which up to now have only been BCG or BCG containing regimens.

DR. TALAMINI: Dr. Bhutani.

DR. BHUTANI: Yes, I have a few questions. One is on is there any data -- we're talking about survival. Is there any data before, for example, BCG was -- became involved, about the progression of transitional superficial bladder cancer in terms of mortality and the progression rate without treatment. Of course, at this time, it may not be ethical to do a study like this when there is treatment but when there were limited treatments out there, any older studies on this?

DR. O'DONNELL: The best study I'm aware of was for a relative uniform group of patients that had carcinoma in situ, and this is, as you all may know, one of the clear indications for BCG use in the United States. In fact, it's acknowledged by everyone essentially in the world, this is the number one treatment.

The studies from the Mayo Clinic was before the BCG era and they recorded a progression rate of about 7 percent per year regardless of when they got

their cystectomies. In general, the death rate is 50 percent of the progression rate because half the patients that have muscle invasive disease die of it. That gives you just a general idea of what a rate would be.

Now, there have been recently an attempt to define risk tables of progression and recurrence based on the EORTCs, a risk calculator which is now available online, and that does give you an idea of what the expected progression rate is. It's generally about 5 to 10 times lower than the recurrence rate, and can give you a ballpark of what relative differences in the order of magnitudes are between recurrence and progression.

DR. BHUTANI: Thanks.

DR. GROSSMAN: The other point is that T1 disease is associated with the 30 percent risk of progression to muscle invasive disease. So that's not high enough to say that everybody that walks in the door with T1 should have an immediate cystectomy, but it's enough to say they deserve an aggressive course of therapy, and if they don't respond promptly and still have T1 disease, then you should have a very short fuse for proceeding with a cystectomy, not continuing with therapy indefinitely.

DR. DONATUCCI: Let me just ask you further about that. So you give an aggressive course of therapy. They don't have recurrence disease, but is there evidence that actually, other than preventing the recurrence when you go back and biopsy, does the percent progress change? Does the percentage change? Is it still 30 percent? In other words, you just said 30 percent of T1 disease progress.

DR. GROSSMAN: Yes.

DR. DONATUCCI: And therefore they deserve aggressive therapy.

DR. GROSSMAN: Yes.

DR. DONATUCCI: And you reduce their percentage of recurrence but does that actually -- is there data now to say and then subsequently you have also reduced their chance of progression from 30 percent to a lower number?

DR. GROSSMAN: There's data with T1 patients in this series. There's data with T1 patients in other series which show that BCG is better than mitomycin for decreasing the recurrence rate of T1 disease. Similarly, with this trial which included high-risk patients, many of which had T1, again treatment with Synergo was better than mitomycin in preventing disease recurrence but having

large numbers of T1s in a single series showing that treatment is better than no treatment, I don't think that has been looked at. So it's basically one treatment versus something else.

DR. DONATUCCI: I don't want to leave you with the impression that I'm not in favor of treating these patients. I'm just trying to point out that the data, the evidence just isn't there. And I'm not saying you shouldn't treatment but the evidence isn't there.

DR. GROSSMAN: Right, and I wish the data was stronger but that's why there's been several meta analyses done which show that BCG does prevent progression, and the problem is you need large numbers of patients and long follow-up and even big large randomized trials frequently don't address all the questions that we like to rigorously address, and I'm as skeptical about meta analysis as anybody else but frequently that's what we have to resort to, to try and answer some of these difficult questions which haven't been rigorously addressed by the existing literature.

DR. TALAMINI: Yes, sir.

DR. BHUTANI: My follow-up question is again regarding, we've talked about survival data or

lack thereof in superficial bladder cancer. What I'd like to understand is short of survival, 30 percent of people will likely progress to muscle invasive bladder cancer. Then they may need cystectomy or other therapies that are more aggressive. I'd like to understand the morbidity to the patient when they have a muscle invasive cancer, their quality of life, sexual, urinary function and so on and what happens?

DR. TALAMINI: Just to clarify. Do you mean between these two therapies, cystectomy versus what's being --

DR. BHUTANI: In the sense that we are talking about whether we should treat superficial bladder cancer at all because we, you know, BCG they're saying prevents progression but it doesn't affect survival or we don't know if it affects survival but if a patient say, didn't have BCG and his tumor or her -- his tumor would be more likely to progress, then what would be the effect without any treatment on a patient with superficial bladder cancer and morbidity and quality of life?

DR. O'DONNELL: Okay. So getting back to the survival issue, again we're encumbered by the fact that it's a small event rate. I will tell you that this year's AUA and at the European Association

National Meeting, there actually was for the first time data presented on a large randomized trial of Epirubicin and TURBT versus BCG and TURBT and there was a survival advantage. Now, I know you talk about, well, how many percentage of patients does that affect, and my answer there really would be that it's not so much the absolute number of patients, it's the relative benefit you may get from it. So I would still say that if you look at chemotherapy trials and so forth that, you know, a relative benefit of 25 percent is considered clinically significant, and that's the level at least we're working on with progression.

I'd also make a point that, you know, of older folks and superficial bladder cancer, let's take a more common cancer like prostate cancer and we have been at it for, you know, a decade with hundreds of thousands of patients getting radical prostectomies. We are just now beginning to see in our national statistics a small decrease in the death rate of prostate cancer. It's too early to say whether radical prostectomy is responsible for that, but that's the kind of level of evidence you're asking for, to get these kinds of answers. And so, you know, the real bottom line answer is that

recurrence is a major problem and when patients do progress to bladder cancer, they have their bladders removed, most of them are impotent, if they're men, over 50 percent. You have to wear a bag. At least two-thirds of those that receive a cystectomy in the United States are wearing an appliance and a bag. Granted, they adapt to that. There is a 30 percent complication rate in the early 3 months. There's another 30 percent later on. There's a 2 to 3 percent mortality in high volume centers. It's double that in the community center. All of these are very major issues for patients to undergo. So even if you could prevent a 25 percent progression relative, I would say that that -- and that translates into only half the benefit for survival, that's still a benefit for the whole group. Again, relative is still important for the disease population that you're focusing on.

DR. TALAMINI: So let me just take the privilege of the Chair and again sort of try and draw back from the discussion of long term survival because that's not the question we're being asked today, and we do have a lot of things that we need to cover about what we're being asked today. So with that in mind, Dr. Marcovich.

DR. MARCOVICH: This is more of a methodology question, another one with the practice patterns were at the time this started, but would any of these patients have gotten a single mitomycin at the time of resection and, if so, how would that have affected the outcomes?

DR. WITJES: The answer very simply is no because at the time this study was started, the 101, the 101 -- was not an item at all and still is not in the United States.

DR. TALAMINI: Dr. Redman.

DR. GROSSMAN: Could I just supplement that? The AUA has looked at that issue with the current guidelines. What's not so clear in the published literature but is very clear when you talk to the investigators who have done the studies is that a single does of mitomycin is optimal for low risk patients. It is not nearly as effective in preventing recurrence in intermediate and high-risk patients. So this would not be the target population where a suitable dose of intravesical chemotherapy is likely to afford a long-term response.

DR. TALAMINI: So again, let me take the privilege of the Chair because we're just about out of time for generalized discussion, and there are two

issues still on the table that I think we need to get settled if we can. One is the issue of cystoscopy and the study and it sounded before lunch like there was a difference of opinion or dispute, and I wonder whether between the FDA and the sponsor, that still exists or if that's a settled question. So that's one thing about whether the cystoscopies were, in fact, done by the same investigators in the study. That's number one.

And then, number two, is this issue of the post-market study. It sounds as if the sponsors now have proposed a different plan and since that's one of the specific questions that we're going to address, I wonder if the Panel feels that we need to know a little bit more about that. I do. So perhaps the sponsors could address those two issues.

MS. STERN: I'll address the first issue, but I'm basically just going to repeat what I said before that all the cystoscopies were done by the principal investigators at each of the investigational sites. I don't know where the FDA got other information but maybe they can provide that.

DR. TALAMINI: Response from the FDA?

DR. KANE: I did not bring all of my

supporting documentation with me. So I'm not able to give you a numerical answer to that question. It -- I looked over lunchtime through the published report and through the protocol and at least one of these sources indicated that patients had the option to have procedures performed locally in follow-up, but more than that, I can't give you a specific answer at this time.

I did find an additional reference to Dr. Redman's question about what kind of vital information might be missing and in the sponsor's submission of January of this year, for example, and I think this is page 13 where the comment is made that pathology reports were not available on four patients of the recurrence, the comment is made that these reports were not transcribed to the case report form and therefore were not available for later follow-up, and that would be one example of information that was not able to be carried forward.

DR. TALAMINI: Okay. Thank you.

DR. KANE: I think also that you may have perceived somewhat different numerical consequences of this issue of progression, and I think you have to sort out patients by their baseline risk group. It may be 30 percent of T1s, but it's not anywhere near

that for Tas. Many more patients typically present with Tas. So we're focusing on a subgroup of the overall group. The study, as information is available, did not demonstrate a difference in progression. What type of sample size or population might be necessary to be able to examine that question, I think that's a whole different question to open the door for, that we don't have available for you.

DR. TALAMINI: And the post-market study. Sorry, did you have a response to that?

DR. WITJES: Well, we've been thinking about the different locations, and we thought the same, that sometimes patients are within one hospital looked at, at the OR, and then the other time at the outpatients which is the different location but the same hospital. And with regard to the missing pathology, there were two finally patients with missing pathology, one in the Synergo arm and one in the mitomycin C arm.

DR. TALAMINI: And that post-market study changes or differences from what was in the original packet?

DR. O'DONNELL: So as you probably gathered from the description of the older study, it was

relatively convoluted with non-inferiority for eight different variables with highly prevalent adverse events and low prevalence adverse events and was attempting to compare it with historical control which was the proper control. We realize that that was going to be untenable, and we agree that it's really an unworkable situation and provides data that you have to wonder what it's really telling you. And so we envisioned doing a much more simplified study where we get a reasonable number of patients and provide the kinds of rigorous adverse event reporting so that it can go into the labeling, examine, whatever, the actual usage among the subgroups. Where it would be used in the U.S. would again provide very relevant patient population data so that would, in fact, make it clear where this treatment is indeed working. And I want to reiterate the sponsor is very open to working with the FDA and with the Panel to work on the details of this, to provide the proper data acquisition so that you get the data that you think is critical for this kind of study, and that we remain very cooperative and very open to this kind of suggestion. We just presented what we think is a reasonable and very simplified, very pertinent type of post-marketing strategy, post-marketing

study, and we take that as basically the basis from which to go further on.

DR. TALAMINI: Okay. Dr. Redman.

DR. REDMAN: Yeah, this question I didn't think was relevant, but now I'm thinking it is relevant because I thought I had known that that's what I'm going to ask Dr. Grossman and Dr. O'Donnell and maybe the AUA has this information. I read the AUA Guidelines. This is mitomycin C versus BCG as a standard of care in this country for T1, Ta. You know, my sense was from my group of urologists and Southwest Oncology Group that it's not 100 percent BCG use, because if it is, this becomes relevant. That's why I'm asking.

DR. GROSSMAN: No, it is not. I still treat patient with mitomycin. For the really high-risk patients, the AUA Guidelines recommend BCG and I agree, BCG is appropriate currently for T1 and for carcinoma in situ. For other patients, mitomycin is a reasonable choice, and I do use mitomycin C in some of my patients.

DR. REDMAN: Do we get data from the AUA or Medicare use or anything about what is -- I mean is it known?

DR. O'DONNELL: In the United States, BCG

is used overall two to one versus all forms of chemotherapy, and mitomycin is the most common form of chemotherapy used in the United States. Just to clarify what Dr. Grossman said is that the AUA and EUA Guidelines specify the use of mitomycin as a course of therapy as was used in the control arm for patients with intermediate risk disease or BCG. So that's where the option is, and the reason for that is if you fail mitomycin, you often will respond to BCG, whereas the converse is not necessarily the case. But for the high-risk group, which is the highest risk of progression, only BCG or cystectomy is currently in the Guidelines from both national groups.

DR. TALAMINI: We are running dangerously close to being short on time. Dr. Lippert, another discussion question?

DR. LIPPERT: A quick question. In your pivotal study comparing heated versus unheated mitomycin treatments, was there a difference in serum white count?

DR. KOREN: We did not have any case of mito suppression in 101 and as mentioned before, the levels are far too low to cause anything which was described in this.

DR. LIPPERT: You mentioned the levels, but you never mentioned the white count.

DR. KOREN: No mito suppression, no.

DR. LIPPERT: Thank you.

DR. TALAMINI: So, Dr. Connor, I saw you had your hand up with a question, but I would also ask you to serve the Panel as we move towards beginning to address these specific questions being the statistical expert on the Panel, if you could discuss your opinion of the data that you've seen thus far with respect to the statistical issues.

DR. CONNOR: So, and this gets to the broad question of efficacy versus adverse event rate versus biases that are potentially here. Okay. So I think one thing that was brought up by FDA that I think if I were sitting in your chair, I would have said, so I'm going to say something minor, defend is too strong a word, but it was brought up that seven patients randomized to the treatment group didn't receive therapy and only one patient randomized, the control didn't receive the therapy but because of this mix up then, in fact, those numbers are really five versus three which isn't quite so bad. I'm sorry, didn't receive therapy but withdrew from the study. So seven versus one withdrew from the study.

If we look at how this switching occurred, it's five treatment versus three control withdrew from the study and if we actually look at patients who received at least one treatment course, only two patients randomized to your treatment versus three on the control group, elected to remove themselves from the study. So I think that speaks positively at least that there's not a difference in patients who didn't like being treated by this. So I think that didn't come up clearly, but something I was able to count from this.

I think some of the biases, and this was the question I asked, that I was told was our question to answer, not FDA's question, you know, there are definitely biases here. This isn't the ideal trial, but I've never seen an ideal trial. This may be more or further from the ideal trial than we would like which is why we're a Panel in the first place. But the treatment effect is pretty big, and I think that definitely helps overcome some of these biases. So I think I would punt the question you asked to me to the clinicians on the Panel and ask in particular if you did the post-approval study, and I think that the way that you're proposing to do it is better than the first way because I think the fairest

thing you can do is identify the risks and precisely quantify the risks which your study does much better than the first study in a way that clinicians are going to understand. So the clinicians and their patients can discuss and say, here are the risks in a clear way and here are the benefits.

So I think my key question that I have to ask of the other clinicians up here is what is the risk or what are the cons of approving a treatment, and I ask this without alluding to what my beliefs are, but is the risk or the cons of approving a treatment that looks like it works with quantified risks, some of which we have seen, and it sounds like we all have better quantified risks, so that doctors and patients can discuss a treatment that is available to them and decide if that treatment is right to them, and I say that because it looks like the efficacy is pretty good and understanding that it's smaller than we think, but to me personally probably not. The biases aren't enough to overcome what looks to be efficacious in particular and improves quality of life, if not survival, which I understand is important. So what would the risk be of letting this get to market and letting patients and doctors make their own decisions? So I think

that to me is the bigger question right now than any huge statistical concern I have that would be a problem.

DR. TALAMINI: And I would remind the Panel that we are instructed to only consider this based upon the data that we have and not data that we would get from a post-market study.

So with that discussion, I'd like to move towards addressing the specific four questions that the FDA has put before us. Each of you has a copy of them in written form in your packet, and if we could please show the first question up on the slide.

So I'm going to read from what's in front of me because I can't look back and talk in the microphone. I trust that they're the same.

Question Number 1, Effectiveness. Under 21 C.F.R. 860.7(e)(1), effectiveness is defined as reasonable assurance, based upon valid scientific evidence, that, in a significant portion of the population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

The PMA for the Synergo system presents

clinical data from a single pivotal trial, Study 101, and several additional supporting clinical data sources, the review of which present the following challenges in assessing the effectiveness of this combination product.

Significant limitations exist in the design and conduct of Study 101.1, which when considered collectively, potentially impair the ability to interpret the results and increase the uncertainty of the state conclusions including multiple sources of bias; the absence of structured methods for obtaining pathology samples and recording pathology information; potential variation in mitomycin C exposure between the study groups; and reliance on a small, limited study population to perform the risk/benefit analysis and generalize the study results to the general U.S. population.

The supporting clinical data sources were not designed to provide stand-alone evidence of the safety and effectiveness of the Synergo system for the proposed indication.

So the question then, considering the design and conduct of Study 101.1 and the supporting clinical data sources, please discuss whether the clinical data in the PMA provide reasonable assurance