UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

GASTROENTEROLOGY AND UROLOGY DEVICES PANEL

+ + +

June 25, 2008
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

PANEL MEMBERS:

MARK TALAMINI, M.D.	Chair, Voting Member
MANOOP BHUTANI, M.D.	Voting Member
JASON CONNOR, Ph.D.	Voting Member
PHILLIP DAHM, M.D.	Voting Member
SUSAN J. KALOTA, M.D.	Voting Member
TERRY N. LAYTON, Ph.D.	Industry Representative
FRANCINE STOKES, J.D.	Consumer Representative
CRAIG DONATUCCI, M.D.	Temporary Voting Member
MARGUERITE LIPPERT, M.D.	Temporary Voting Member
ROBERT MARCOVICH, M.D.	Temporary Voting Member
BRUCE REDMAN, D.O.	Temporary Voting Member

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

NANCY BROGDON, M.D.
Director, Division of Reproductive,
Abdominal and Radiological Devices

JEFFREY COOPER, D.V.M.
Veterinary Medical Officer,
Gastroenterology Renal Devices,
Executive Secretary to Gastroenterology
and Urology Devices Panel

MEGAN MICKAL
Biomedical Engineer, Gastroenterology and Renal
Devices, Executive Secretary in training to
Gastroenterology and Urology Devices Panel

DANICA MARINAC-DABIC, M.D., Ph.D.
Chief of Epidemiology,
CDRH, Office of Surveillance and Biometrics

NILSA LOYO-BERRIOS, Ph.D.
Epidemiologist,
Office of Surveillance and Biometrics

DONNA-BEA TILLMAN, Ph.D.
Director, Office of Device Evaluation

FDA PRESENTERS:

JOHN BAXLEY, M.S.
HECTOR HERRERA, M.D., MPH
ROBERT KANE, M.D., FACP
XUEFENG LI, Ph.D.
SHAOKUI WEI, M.D., MPH

SPONSOR REPRESENTATIVES:

YAGEL KOREN, M.D.
MICHAEL O'DONNELL, M.D.
AHAVA STEIN
FRED WITJES, M.D.
H. BARTON GROSSMAN, M.D.
LISA DEUTSCH, Ph.D.

OTHER PARTICIPANTS:

ROBERT LIPMAN

INDEX

INDEX

M E E T I N G

(8:00 a.m.)

DR. TALAMINI: Good morning, everybody. I would like to call this meeting of the Gastroenterology and Urology Devices Panel to order. I'm Dr. Mark Talamini, Chairperson of this Panel. I'm a gastrointestinal surgeon, the Chairman of the Department of Surgery at University of California, San Diego.

If you haven't already done so, please sign the attendance sheets that are on the tables by the doors. If you wish to address this Panel during one of the open sessions, please provide your name to Ms. AnnMarie Williams at the registration table.

If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to FDA, please arrange to do so with Ms. Tobey Lowe. Tobey, if you could stand. There's Tobey. Thank you.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

No one from the public or the press is allowed into the Panel area up here at anytime during the break or during the conduct of this meeting, and I would remind everybody to please silence your cell phones for the smooth conduct of the meeting.

Dr. Cooper, the Executive Secretary for the Gastroenterology and Urology Devices Panel, will make some introductory remarks. Dr. Cooper.

DR. COOPER: Thank you. I'm now going to read the Conflict of Interest Statement, the FDA Conflict of Interest Disclosure Statement, with a particular matter involving specific parties.

The date of the meeting is June 25, 2008.

The Food and Drug Administration is convening today's meeting of the Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and consultants of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with the federal ethics and

conflict of interest law is covered by, but not limited to, those found at 18 U.S.C. 208 and 712 of the federal Food, Drug and Cosmetic Act, the FD&C Act, are being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this Panel are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meetings, members and consultants of this Panel or special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes

of 18 U.S.C. 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents, royalties and primary employment.

Today's agenda involves the discussion of a pre-market approval application, a PMA, for the Synergo SB-TS 101.1 Device and Mitomycin C, sponsored by Medical Enterprises, Ltd. This drug/device combination product is designed to prevent the recurrence of bladder cancer. Synergo SB-TS 101.1 Device with Mitomycin C is indicated for use for prophylactic treatment of recurrence in patients following endoscopic removal of Ta to T1 and G1 to 3 superficial transitional cell carcinoma of the bladder, STCCB. Synergo and Mitomycin C treatment is clinically indicated for STCCB patients of intermediate and high risk.

This is a particulars matter meeting which specific matters related to the PMA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. 208 and 712

of the FD&C Act.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Terry Layton, Ph.D., is serving as the Industry Representative acting on behalf of all related industry and is self-employed by Laytech, Incorporated.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which a FDA participant has the personal or imputed financial interest, their participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

Now, I will read the Appointment to Temporary Voting Status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, and amended August 18, 2006, I appoint the following as voting members to the

Gastroenterology and Urology Devices Panel for the duration of this meeting on June 25, 2008: Craig Donatucci, M.D., Marguerite Lippert, M.D. and Robert Marcovich, M.D.

For the record, these people are special government employees and are consultants to this Panel or another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This was signed by Daniel G. Schultz, M.D., Director, Center for Devices and Radiological Health and dated May 28, 2008.

I'll also read a second appointment to temporary voting status, and that is pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and amended August 18, 2006, I appoint Bruce G. Redman, M.D., as a temporary voting member of the Gastroenterology and Urology Devices Panel for the duration of the meeting on June 25, 2008.

For the record, Dr. Redman serves as a consultant to the Oncologic Drugs Advisory Committee

of the Center for Drug Evaluation and Research. He is a special government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

This was signed by Randall W. Lutter, Ph.D., Deputy Commissioner for Policy, on May 13, 2008.

I would also like to note the absence of our Patient Representative, Col. James D. Schultz. He was enthusiastic about attending the meeting to offer his viewpoints as a patient. Unfortunately, his family informed us that he passed away on May 22nd. His son, Jim Schultz, Jr., told us that, "I know that he appreciated the opportunity to return to the medical community some measure of his appreciation for the wonderful care he received over the years."

Before I turn the meeting back over to Dr. Talamini, there are a few general announcements.

Transcripts of today's meeting will be available from the Free State Court Reporting. Their contact information is available as a handout at the registration table outside.

Information on purchasing videos of today's

meeting can be found on the table outside the meeting room also.

Presenters to the Panel who have not already done so should provide FDA with a hard copy of their remarks including any overheads.

I'd like to remind everyone that members of the public and press are not permitted around the Panel area, beyond the speaker's podium.

The press contact for today's meeting is Peper Long.

And I request that the reporters wait to speak to FDA officials until after the Panel meeting.

Thank you. Now, Dr. Talamini.

DR. TALAMINI: Again, good morning, everyone. At this meeting, the Panel will be making a recommendation to the Food and Drug Administration, the FDA, on the pre-market approval application, PMA, P010045 for the Synergo SB-TS 101.1 Device and Mitomycin C for Medical Enterprises, Ltd.

Before we begin, I would like to ask our Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position and your affiliation, and I would remind, a technical detail for those of us at the table, when you push your

button, we can only have four buttons pushed at a time. So when you're done speaking, please push it and turn it off again, and if we could begin over to the right with Ms. Brogdon.

MS. BROGDON: Good morning. I'm Nancy Brogdon. I'm not a member of the Panel. I'm the Director of FDA's Division of Reproductive, Abdominal and Radiological Devices.

DR. MARCOVICH: Good morning. I'm Robert Marcovich. I'm a urologist at the University of Texas Health Science Center in San Antonio.

DR. DONATUCCI: Good morning. Craig Donatucci. I'm a urologist at Duke University in North Carolina.

DR. LIPPERT: Good morning. I'm Marguerite Lippert. I'm a urologist at the University of Virginia in Charlottesville, Virginia.

DR. BHUTANI: Good morning. I'm Manoop Bhutani. I'm a gastroenterologist at MD Anderson Cancer Center in Houston.

DR. CONNOR: Good morning. I'm Jason Connor. I'm a biostatistician. Basically I design clinical trials typically in the regulatory environment, and I work for Berry Consulting in Orlando, Florida.

MS. MICKAL: Good morning. I'm Megan Mickal. I'm a biomedical engineer in the Gastroenterology and Renal Devices Branch, and I'm the Executive Secretary in training.

DR. COOPER: Good morning. I'm Jeff Cooper, veterinary medical officer in the Gastro Renal Devices Branch of the FDA and also the Executive Secretary for the Gastroenterology and Urology Devices Panel.

DR. TALAMINI: Again, my name is Mark Talamini, Panel Chair, gastrointestinal surgeon employed at University of California, San Diego, as the Chair of the Department of Surgery.

DR. DAHM: Good morning. My name is Phillip Dahm. I'm a urologist at the University of Florida in Gainesville.

DR. KALOTA: Good morning. I'm Susan Kalota, private practice, urology, in Arizona.

DR. REDMAN: Good morning. Bruce Redman, Medical Oncologist, University of Michigan, Comprehensive Cancer Center.

MS. STOKES: Good morning. I'm Francine Stokes, Esquire. I'm an assistant to the President of Morgan State University for Government Relations.

DR. LAYTON: Good morning. I'm Terry

Layton, a biomedical engineer. I'm the Industry Panel member here today and also from Laytech located in Chicagoland area.

DR. TALAMINI: Thank you, everyone. Next Danica Marinac-Dabic, I hope I didn't hurt that too badly, from the Office of Surveillance and Biometrics, would like to provide the Panel with a Post-Market Studies Update. Dr. Marinac-Dabic.

DR. MARINAC-DABIC: Thank you. Good morning, ladies and gentlemen, Dr. Talamini, Dr. Brogdon, distinguished members of the Panel.

My name is Danica Marinac-Dabic. I am the Chief of the Epidemiology Branch at the CDRH's Office of Surveillance and Biometrics, and the Epidemiology Unit is in charge of the review, monitoring and tracking of post-approval studies also known as conditional approvals that is. We're also in charge of post-market surveillance studies also known as Section 522 studies, another way how the FDA can ask for additional post-market data, and also our unit is in charge of FDA funded epidemiologic research studies, which are the studies that are independently conducted by the FDA to obtain additional post-market data on the approved products.

As members of the CDRH Expert Advisory

Panel, you play a crucial role in our decision making in terms of approval of medical devices and also very often you make recommendations for so-called condition of approval studies or post-approval studies that are imposed by the PMA Order, and I know that this afternoon, you're going to be also engaging in some of the discussions about the post-approval study for the product that is under discussion today.

So having that in mind, I would like to give you today an update on significant changes that had occurred in the CDRH Post-Approval Studies Program during the last two to three years and also specifically to give you a brief snapshot of what urology devices post-approval studies we currently have in place and what is their status. I'm not going to go into a lot of details but just to give you an idea of the information that is publicly available on the status of our studies.

As you know, FDA can impose post-approval requirements at the time of the approval of the PMA, and this slide just lists that authority, and just to make sure that we all understand that these studies are done for continuing evaluation and reporting of the safety, effectiveness and reliability of the device for its intended use.

And this is certainly very important statement because we would like to know up front that post-approval studies should not be used to address any pre-market questions. Anything that is essential for the establishment of the reasonable assurance of safety and effectiveness of the product has to be demonstrated by the pre-market data.

This is just a summary of the need for post-approval studies and, you know, during your review of the submitted package, you know that, you know, the sponsors usually gather a lot of pre-market information that help you, the Panel, decide what kind of recommendations you're going to make.

However, there still could be some unanswered post-market questions for which post-approval study route may be suitable. And these are some of the reasons why we need the post-approval studies. For example, we need to learn longer term performance including the facts of re-treatments and product changes. This is something for which post-approval study can be asked for.

Now, as the devices are moving from the highly trained and best clinical centers as is usually chosen by the sponsors during the pre-market trial, we would like to know how these devices are

performing in the community type of practices. And sometimes the effectiveness of training programs can be assessed by the post-approval studies, or if the pre-market data did not have sufficient information of subgroup performance, we can ask for the post-approval study to address that question.

And in our intent to reduce the burden on the sponsors and provide the least burdensome mechanism for them to demonstrate reasonable safety and effectiveness, we also consider post-approval studies to obtain the longer term data in the broader population for the intended use.

And very often Panel members bring their thoughts, based on their experience, to us that we didn't think of as the peer review team, and we would like to incorporate those in the post-approval studies.

It's very important again to state that the objective is to evaluate the device performance and potential device-related problem in a broader population over an extended period of time after the pre-market establishment of the reasonable assurance of the device safety and effectiveness, and post-approval studies should not be used to evaluate unresolved issues from the pre-market data.

And again, it's always the balance between less burdensome evidence to support pre-market approval and assurance of continuous product safety and effectiveness.

Well, a couple of years ago, we looked into our post-approval studies across the Center, and after this evaluation, we, the Center, had decided to start major post-market transformation in this area with the following major goals. To enhance scientific rigor of post-approval studies and also to establish and maintain the accountability for the post-approval study commitments. We also wanted to build the post-approval studies information management system and to build a bridge between the pre-market information and the post-market information and certainly to feedback what we learn in the post-market arena to our pre-market colleagues that are reviewing the new PMA submissions.

And, finally, we wanted to increase our transparency with the public, to make sure that all interest of stakeholders have timely access to the publicly available information on the status of the post-market studies.

So these are the major areas that we tackle in this post-market transformation effort. We have

changed the oversight. We developed a tracking system. We made major changes in the review of post-approval studies. We issued a guidance document. We developed a web posting page that lists all the post-approval studies, and we started this Post-Advisory Panel Updates, again with an intent to give the Panel the most recent information about these changes. And we undertook a comprehensive strategist to build public health partnerships with the clinical communities, with manufacturers, with CROs, academia, to help us better understand the design and the conduct of post-approval studies.

So historically, post-approval studies were housed in Office of Device Evaluation in the Review Divisions, and in 2005, the initial transfer had occurred and completed in 2007, where the post-approval studies review was integrated into one post-approval studies program housed in the Office of Surveillance and Biometrics. And again, the epidemiology group was the one who was given the charge for this review and monitoring.

In addition to the oversight changes, as I said, we have developed and instituted automated tracking system which is based on the timelines that are agreed upon between the sponsors and the FDA at

the time of the approval. And, based on that timeline, our tracking system is designed to make sure that we keep track of all the submissions, when they come, and make sure that we remind sponsors that if they do not comply with our commitments, everything is posted on our webpage, and I'm going to talk about that in a little bit.

So these are the major changes that have occurred in the pre-market review process.

Again, in the past, the epidemiology group was not part of the review process, and we would have received information about the approved product and then designed the post-approval study, helped to work with sponsors on the design of post-approval studies.

The major change had occurred when an epidemiologist was added to each PMA review team. So now we are part of the pre-market review process, and our role is to identify those reasons for the post-approval studies, the rationale for the post-approval studies and then work interactively with the sponsor to help them design good study that is based on good solid hypothesis, that has good, clearly stated objectives and certainly our goal is to increase the scientific rigor of those studies. And you will hear also, if the device goes to the Panel, the

epidemiologists will be part of the Panel presentation as well.

The goal is certainly to finalize the protocol before the product is approved. So once the approval order had been issued, the sponsor is ready to go and apply for the IRB approvals and can start the study.

What happens when the product is approved? Again, the epidemiology group has the lead on all post-approval study reports and supplements that involve changes to the protocol, but we make sure that our pre-market colleagues stay informed and engaged in this review process, and this strategy is designed to actually couple the epidemiologist's expertise and observational study design and the technical expertise that resides in our pre-market office.

We issued a guidance document in 2006 and with a slight revision in August of 2007, and in that guidance document, we clearly stated what are the reporting status definitions. As you can see, they can range from on time, overdue or report already received, and also these are our study status definitions, and all of these things are also available in our webpage, with a goal to increase the

transparency with the public.

This is the webpage that went live in on April 6 of 2007, and all the reporting schedule status and post-approval study status is on that webpage.

We currently have over 120 studies, but only those that initiated post-2005 are on the webpage, and this is how the webpage looks like. You can see there is an application number and the name of the applicant, device name, also the medical specialty. We also have study commitments listed there, and when the protocol was approved and what is the study population under the study and what is the current status.

This database, this is linked also the PMA database. So you can also search for more information out there. And this is constantly updated based on the feedback from our stakeholders.

Now, as I said, it's very important to close the role certainly with Panel members as they are part of our decision making process, and we instituted these two initiatives, to prove this general post-approval study updates at the beginning of every Panel meeting. So first update was presented in November 2007, and since then, we have

these updates at every Panel meeting. Those are so-called general updates.

If there is a specific issue that we would like the Panel to discuss, then we have a different strategy. We have so-called specific post-approval study updates, and they're a little bit more formal. We invite the sponsor to give their presentation, and we are also giving FDA perspective on this, and then we come up with questions that we would like to get Panel's input, but certainly that's a more joint effort between the sponsors and the FDA.

And as I said, we started huge effort and devoted significant amount of resources to build public health partnership. This is just an example of first in series of conferences that we cosponsored with the Food and Drug Law Institute last year, and there are two that are being planned for this year and next year, where we invited the prominent members of a clinical community also, you know, contract research organizations, certainly lawyers, manufacturers, Panel members, to talk about post-approval studies and give us their feedback.

I would like also to tell you that we are looking into innovative approaches, how we can design those studies better and how we can use existing

databases to satisfy some of the post-market study commitments.

Now, very briefly, I'm not going to go into a lot of details, this is, you know, how many PMAs, original PMAs and Panel track supplements were approved in the period from 2005 to 2008, and how many of those, as you can see, there were 5 approved original PMA supplements with the post-approval study. This is for all gastroenterology and urology devices, and this is how the picture looks like for the urology devices only. We have four ongoing post-approval studies issued, at the time of the three PMA approvals, and this is the list of the urology devices for which the PMA approval asked for the post-approval study. I'm sure that many of you had participated in the discussion and the recommendations. So I'm not going to go into a lot of details.

This is just a brief summary of what type of study design we are using. Certainly, there are various design strategies that we can use in the post-approval study. Sometimes we use the registry as a framework to -- the study, and this is one example, and you can see here what the objectives of this particular registry is and what type of end

points and what type of duration we're talking about here, also to say that these studies currently listed on time on our webpage.

For Macroplastique, we have two different post-approval study commitments. One is the real time observation of safety and effectiveness registry, again with 275 subjects, to look at the durability of treatment effect and impact of re-treatment, 5 years again follow-up, and this study is on time as well.

This is the second piece for Macroplastique, which is enhanced surveillance system. Again, we try to compliment the post-approval studies with the enhanced surveillance system to try to get gather as much as possible of the post-market data.

And finally, the -- this study was listed overdue until recently, and the protocol was just approved last week. Again, this was an example when there were some challenges on implementing and starting and drawing patients into the study, and we had revisited our original approval order and worked with the sponsor to design the study that will address your post-market questions but would be less burdensome to conduct.

And again this is just a summary of what type of study designs we use. As you can see, we have registries or perspective one-arm studies or enhanced surveillance system in this case, and as far as how diligent the sponsors are in terms of sending their reports to the FDA, there were two reports that were overdue, but they were received and they're marked as such on our website, and two other reports are on time.

And studies are on time and, you know, for three of those studies and the protocol recently approved which means the study will start very soon.

And this is again just a recap and this is my last slide. This is our vision. We would like for the Panel to know that post-approval studies, our vision is to have studies that answer only important post-market questions, not just the questions that the FDA staff may be curious about but really the ones that are important public health questions because we understand the burden and the cost and the effort that the sponsor have to put into making these studies success. We would like those studies to be realistic and founded on good science, and timely, accurate and provide use for results that we can then incorporate into labeling changes.

We also would like reports to be clearly identified, effectively tracked and we certainly are committed to keep our stakeholders apprised. I would like again to say that nothing can be accomplished in terms of this vision if we do not continue cooperating with our pre-market colleagues. That's a key for our success, and if we continue with this effort, we believe that the enforcement actions will be rare. We ask for those when it is necessary but by proactively addressing these issues, I think we are going to have not that frequent cases when we need to do the reinforcement. Thank you very much.

DR. TALAMINI: Thank you, Dr. Marinac-Dabic. That was extremely helpful.

We'll now proceed with the open public hearing portion of the meeting.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believe that it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, the open public hearing or industry speaker, at the beginning of your written or oral

statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if know, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Prior to the meeting, we have received one formal request to speak during today's open public hearing sessions. Our speaker is Mr. Bob Lipman. Please come forward to the microphone. We ask that you speak clearly into the microphone to allow the transcriptionist to provide an accurate record of this meeting, and we have about five minutes to stay on track. Mr. Lipman.

MR. LIPMAN: Good morning. My name is Robert Lipman. I am representing the Bladder Cancer Advocacy Network, and I have no financial relationship with the sponsor.

Thank you for the opportunity to speak here

today and to share my experience as a bladder cancer survivor and patient. Like many who are ultimately diagnosed with this disease, I was initially misdiagnosed in 2003 by my internist before my urologist was able to confirm with a cystoscopy and bladder biopsy that I indeed did have bladder cancer.

After having the cancer removed and some complications with bleeding, I received BCG treatment once a week for six weeks. I did not experience any side effects from the BCG treatment although it is never pleasant to get treatment through a catheter.

A subsequent bladder biopsy showed that the cancer had returned. Since BCG was not effective in preventing the cancer from returning, an alternative treatment choice at the time was BCG+Interferon. A study had recently been published indicating that BCG and Interferon could be effective in patients who failed with BCG alone. BCG+Interferon is not an FDA approved treatment.

I had much more severe side effects with BCG+Interferon including intense irritation of my bladder and extreme exhaustion. After getting treated with BCG+Interferon once a week for six weeks, another bladder biopsy showed that the cancer had returned and again it was removed.

After failing with BCG+Interferon, what were my treatment choices? I received a second opinion at Johns Hopkins, and we made the unusual decision to repeat the BCG+Interferon even though it hadn't been effective.

Fortunately, the next biopsy in October 2005 was clear, and I've been cancer free since then. However, bladder cancer requires frequent monitoring and treatment. Since then I have undergone many more bladder biopsies and almost 30 more BCG+Interferon treatments.

Another side effect of BCG with Interferon was dealing with my health insurance company. Interferon requires special approval by the insurance company, and approval is good for one year. After having been approved for several years, I was denied approval because the insurance company said that it was not a FDA approved treatment. As a federal employee, I was able to file an appeal with the Office of Personnel Management who overturned the insurance company's decision.

What happens if my bladder cancer returns? What are my treatment choices? Of course, I want to avoid at all cost having my bladder removed. I and many other bladder cancer survivors and patients need

more safe and effective treatment choices. I urge the FDA to encourage the development of new treatments for this disease and to work quickly to approve those treatments that are proven to be effective.

While every cancer patient's story is unique, there are several common issues that many of us in the bladder cancer community share. The disease is quite prevalent, currently the fifth most commonly diagnosed cancer in the United States, fourth among men. When I was diagnosed, I had never even heard of it even though it is so common. Despite its prevalence, many of us go undiagnosed or misdiagnosed before finding out that we have bladder cancer. A late diagnosis increases the chance that the cancer will have invaded the bladder muscle wall, and unfortunately medical treatments for muscle invasive disease are limited and for most patients, the standard of care is removal of the bladder as well as the prostate in men, a life altering surgery.

Bladder cancer has a very high recurrence rate, and bladder cancer patients must have ongoing rigorous checkups and testing with respect to follow-up care and, if necessary, treatment for recurrence. Patients and their families bear the psychological

burden of knowing that the bladder cancer often comes back and that there are limited treatments for the disease, so that if the treatment does not work, major life altering surgery may be the only option.

I began volunteering for the Bladder Cancer Advocacy Network, BCAN, in 2005, to help raise the awareness about bladder cancer and to be part of the push for more research so that early detection becomes a reality and that new treatment options are available to patients who have been diagnosed.

BCAN is the first and only national organization dedicated to raising awareness, educating patients and clinicians and advocating for more research into treatments for this disease. BCAN's Scientific Advisory Board has more than 35 bladder cancer specialists, all urologists, oncologists, radiologists or pathologists, representing major cancer centers in the United States and Canada.

On behalf of BCAN, and for all who are currently living with bladder cancer, and for those who have yet to be diagnosed, again I urge the FDA to encourage the development of new treatments for the disease and to carefully evaluate this application to determine whether to recommend to the FDA that

Synergo should be approved as another treatment for bladder cancer. Thank you.

DR. TALAMINI: Thank you very much, Mr. Lipman. Is there anyone else in the audience who would like to address the Panel at this time? Please raise your hand and come forward to the microphone. I'm not seeing any hands.

We will proceed with the sponsor presentation for the Synergo SB-TS 101.1 Device and Mitomycin C.

I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel.

We will begin with the sponsor presentation. The first presenter is Dr. Yagel Koren, Medical Director for Medical Enterprises, Ltd. Dr. Koren.

DR. KOREN: Thank you very much, and good morning. I would like to use this opportunity to thank the FDA for giving us this opportunity to show here today and the distinguished members of the Panel for giving the time and effort to be here with us today.

I would present the introduction for this PMA approval. Our presenters today would be Professor Michael O'Donnell who is the Director of Urologic Oncology at the University of Iowa Hospitals and Clinics, Professor Fred Witjes from the Department of Urology in Radboud University, Nijmegen Medical Center, in The Netherlands, Professor Barton Grossman who is from the Department of Urology at the University of Texas, MD Anderson Cancer Center, Ms. Ahava Stein who is a regulatory consultant for Medical Enterprises, and myself.

The order of our presentation today will be first the introduction which will be given as I said by myself. Later on, a brief overview of the disease and current treatment options will be given by Professor Michael O'Donnell. Device description and overview of the clinical studies will be presented by Ms. Ahava Stein, and later on, the overview of the clinical studies will be presented by Professor Witjes. Finally, Professor Barton Grossman will give an overall summary of our application, and just to add a note, we have been asked by the FDA to prepare a plan for possible post-approval study should the Panel recommend such one, and this plan will be presented again by Professor Michael O'Donnell.

In my introduction, I will give you a few short notes on the device itself, the history of the company and the history our previous study, Study 101.1.

About the device. As we know, intravesical chemotherapy has been widely used for a decades, both in the U.S. and outside the United States for the treatment of non-muscle invasive bladder cancer. But its limited frequency gave reasons to find methods to improve its efficacy. This thing in turn led to the development of the Synergo hyperthermia device in San Raffaele Hospital, which is located in Milan, in Italy, back in the 1990s.

Our hyperthermia device is designed to heat the bladder walls with this to increase the effect of mitomycin for the treatment of bladder cancer.

Our history, in 1994, our pivotal study has begun. It begun as the collaboration of three investigators as an investigator-initiated study in three academic centers in Italy and Israel. Only three years later, Medical Enterprises was formed and acquired the technology and the sponsorship of this academic, scientific research. CRFs were then formed and all the previous data was transcribed into these newly formed CRFs. From 1997 until the end of the

study in 2001, all the data was already prospectively registered on the CRFs.

In 2000, about eight years ago, our Synergo device received the CE mark in Europe and the approval of the Israeli Ministry of Health and ever since is routinely used to treat patients with bladder cancer in Europe and in Israel.

What about our company? Medical Enterprises is a small company, and it has Synergo as its only product. Should this PMA be approved, we plan on cooperating with a local American company to introduce the device into the United States.

Thank you for your attention, and now for a few words on the disease and current treatment options, I would like to call on Professor Michael O'Donnell. Thank you.

DR. O'DONNELL: Thank you, Yagel. Mr. Chairman, members and guests, it's my pleasure to talk to you about the disease of bladder cancer. Just to tell you about myself, I am a urologist. I specialize in urologic cancer, particularly in bladder cancer. I've served on committees with national trials groups such as CALGB, to advise them on trials for bladder cancer, and I've also reviewed the AUA Guidelines Panel as a peer reviewer. I have

been a consultant for Medical Enterprises for about three years, but I have no financial stake in the company per se.

Let me tell you a little bit about the disease. The bladder is obviously a cavity, and it's lined by a surface epithelium, and it's this epithelium that becomes malignant. And bladder cancer occurs in three basic forms, a surface spreading disease known as carcinoma in situ. This is the minority, about 5 to 10 percent, and this is a disease that is not being handled by the Synergo device.

The vast majority of cases are this papillary exophytic growth in the bladder that projects into the lumen of the bladder. This is at least two-thirds to three-quarters of the cases of bladder cancer.

And the third type is this nodular form which is a more ominous form. It can be in the mucosa, the submucosa and eventually invade into the muscle. This is the type that essentially kills patients.

There are two major distinguishing factors when we talk about bladder cancer. One is the stage, and that is the depth of invasion of the disease, and

second is the grade which is the degree of aggressiveness of the cancer. The stage is given in a TMN, tumor, node, metastasis staging system as a group here that includes CIS or Tis, Ta disease limited to the mucosa, T1 disease that goes into the submucosa. And we distinguish this group as being the superficial group mostly because we can resect this from an endoscopic approach. Anything beyond that, including invasion into the muscle or through the muscle into the fat or into other adjacent organs, is the muscle invasive category that occupies about 25 percent of the presentations of bladder cancer. The Synergo is limited to the superficial group.

We also distinguish the grade as I mentioned. I'm just showing you here a picture of low grade, these well-formed cells, papillae versus this more antiplastic example of a high grade cancer. Grade does correlate greatly with prognosis as well and with progression.

Now, bladder cancer is a disease that is not limited certainly to the United States but rather has a certain distribution related to environmental and occupational exposures. And so it tends to be the same in the westernized countries. This is

demonstrating the male instance of bladder cancer in North America. As you can see, a similar color code for Europe, for Israel and for Russia.

Now, the disease is also very similar between the two continents, between the U.S. or North America and Europe with regard to the disease characteristics, that is the percentage of superficial versus invasive, the stage distribution and the grade distribution. Likewise, the treatments are very similar, such that in terms of diagnosis, it's universally diagnosed by a cystoscopy, often office based, and it's universally treated by a procedure of going into the bladder and resecting or removing the tumor as the first initial treatment.

And finally, and probably more importantly, is that the recognition by two of the major governing bodies, first the United States, the American Urological Association, and the corresponding group in Europe, The European Association of Urology, have drafted guidelines that have been recently published in November 2007, for the AUA and in March of 2008, updated for the EAU, that represent consensus of management that are remarkably similar, both in regard how to initially diagnose, biopsy, resect and then apply adjuvant treatment such as intravesical

therapy.

This is the process by which we diagnose bladder cancer. It involves obviously placing a resectoscope through the urethra in this case, through the prostate of a male, and imaging the internal surface of the bladder. This is the Gold Standard and is felt to accurately detect bladder cancer in over 90 percent of cases. We use the same technology then by applying different instruments to actually physically remove the tumors and this is illustrated here in this cartoon but here's a real-time image of a resection occurring through a hot loop, through a papillary projecting bladder cancer here.

The problem with doing surgery though is that most patients recur. In fact, this represents the aggregate results of that analysis from the European community of about 1200 patients with a reasonably good follow-up of about five years, representing that there's an exponential decay curve, which is similar what you see for many cancer treatments, or cancer recurrences, and it levels off somewhere around five years.

If you look at the event rate, the number, the percentage of those cases that occur, most of

them occur early. In fact, over 50 percent within the first year and close to 90 percent in the 2 years, and this is the reason why a 2 year point is a reasonable point to evaluate the efficacy of treatments on this disease.

Now, the high recurrence rate remains a very significant problems, and it's for this reason that adjuvant therapy or additional treatment, intravesical treatment, placing medication in the bladder, have become advocated by both national governing bodies, the American Urological Association and the European Association of Urology, and they've done so according to basically a risk adapted policy, putting patients into categories such that one can apply more universal treatment recommendations so to speak. The AUA does this by giving index patients and the European Association of Urology has formulated actually these three categories here which I put for convenience.

The low risk group, which is by the way not the group that is being treated by Synergo and represents about half of the patients with bladder cancer, are the single, solitary papillary low grade small tumors, the best actors, and they have a recurrence rate of about 40 percent within 2 years,

as opposed to the high-risk group, which has a very high recurrence rate, over 70 percent within 2 years. These include any high grade disease, any grade 3 Ta or T1, any CIS, and a subset of grade 2 T1 disease that a multifocal. And then the intermediate risks which represents about a third of all the patients, and these patients are essentially those that are between the extremes. Any patient that has had a recurrent cancer, that's papillary, non-high grade, any patient with multifocal disease falls into this group or any very large tumors. These are the two groups that are being targeted for the Synergo device.

Now, the guidelines then reflect this risk adapted policy, advocated both in very similar formats by the American Urological Association and the European Association of Urology. So for the low risk group, those small papillary tumors, it's felt that one single treatment of medication, and the most common one in the United States is mitomycin, is given immediately after, within six hours of the urethral resection, transurethral resection, and that's felt to be recommended and sufficient. It's listed as an option and a recommendation respectively for the AUA.

The intermediate group which represents about a third of the patients, includes that first single dose of chemotherapy, more advocated by the EAU than AUA, but relatively recognizes as being an important first step, followed by additional treatment. And here, both the guidelines recommend either mitomycin C or equivalent chemotherapy or BCG, often with a maintenance program, about 1 year with BCG and 6 to 12 months for chemotherapy.

And finally we come to the high-risk group which represents a subset, 15 percent, nonetheless the most important ones because these are the ones that go to progression. And here, the options really are only BCG with maintenance, or viable options, or cystectomy, removing of the bladder. Now, it used to be in the original guidelines in 1999 and 2002, that mitomycin C was listed here. That was until we had sufficient information to understand that the results are significantly inferior to BCG unless only BCG is the non-surgical alternative for these high-risk patients.

Unfortunately, even the best treatment that we have, have serious limitations especially in terms of efficacy. This graph represents a large southwest oncology group study that was performed in the early

nineties, and what it shows here is a randomized trial of BCG versus mitomycin C. It includes a small percentage of patients with CIS but nonetheless these results are representative of what happens also in the U.S., that is patients relapse early and then there is a plateau somewhere around two years or so.

And in this case, although there is a strong difference between BCG and mitomycin, in fact, for this reason, the study it shows statistical significance. It was actually even stopped early as part of an interim analysis, and I bring this up because this study, in fact, recapitulates some of the issues and the points that you'll see in the Synergo program as well.

And these points include, number one, the study was not a FDA design study. It wasn't one brought to the FDA for approval, BCG, though the data was used retrospectively to submit an approval and for which BCG gained an approval for use against papillary cancer.

Number two, it was stopped prematurely because the safety analysis indicated that there was such a significant difference here that it was unethical to continue it any further.

Number three, is mitomycin C, although it's

not a FDA approved, recognized drug for this indication, was actually used as part of the indication to FDA and accepted as such.

And four, these studies were not blinded, in fact. Studies of this nature, intravesical therapy, to my knowledge, have never really been blinded, and I know that will become an issue that is raised later on.

The final point is that about half of these patients do represent the Ta grade 1 tumors, and if you take those out, both curves drove by about 10 percent. So, if anything, these curves are a little bit optimistic in terms of what you can expect from this form of therapy.

The second major problems with the forms of therapy that we have right now relates to toxicity. You don't get something for nothing essentially. I've made two major comparisons here between mitomycin C and BCG because these are the most relevant issues that we talk about today. As you can see, the toxicity can be related to local toxicity which is mostly frequency, dysuria, irritative symptoms, so-called urinary tract symptoms including hematuria, incontinence and so forth. Systemic symptoms, fever, flu-like symptoms or arthralgias,

skin rash, infectious related issues including bacterial cystitis or UTI, and the continuation rate or treatment discontinuation rate, incomplete or interruption.

First, notice a couple of things. Wide ranges from multiple studies, this was a table done as part of the comprehensive analysis by the 1990 AUA Guidelines Panel, represented the most complete analysis of the literature at the time, wide ranges throughout the studies. In general, a high amount of lower urinary tract symptoms for both mitomycin C and for BCG but generally higher for BCG by about 50 percent, a significant rate of hematuria as well, 16 to 29 percent. Some of the ranges here are up to a third of the patients. Bladder contracture which is a loss of functional capacity of the bladder, 5 percent in the mitomycin C group alone, a small amount in BCG. Generally more systemic fever-like symptoms with BCG which we expect, you know, from therapy but nonetheless some in the mitomycin group. Skin rash more prevalent in the mitomycin group.

Here I've highlighted the incidence of what I would call more serious side effects, and the problem with BCG is that it's a live, though attenuated microbacteria. We give 10 to the 8th

organisms in the bladder once a week for 6 weeks. Some of it can get into the blood stream and cause serious infection, and that serious infection rate is approximately 5 percent and includes some systemic organ manifestations as well as more specific ones like rumenitis.

And finally as you can see with both therapies, there is a real discontinuation or interruption rate that hovers around 10 percent. There are very rare cases, by the way, of lethal consequences of BCG, an overwhelming TB-like infection. Fortunately, they're relatively rare but they remain in the back of everyone's mind that gives BCG.

Now, bladder cancer, you've heard a little bit from our public speaker, is a very significant disease, and just to put this in perspective, there are about 69,000 new cases expected this year in the United States. That's just the tip of the iceberg because for every patient with a new diagnosis, there are 9 to 10 more patients living with the diagnosis. So the estimate is over 500,000, half a million, in the United States with this disease. About 14,000 cancer deaths.

Bladder cancer is also not appreciated that

it is extremely costly. Patients who live a long time have multiple treatments as you've heard about and the average cost is estimated to be somewhere between 100 and $200,000 per patient from the time of diagnosis to death from whatever cause.

This results in or is a reflection of this, many procedures in the U.S., 300,000 over, for just the surgical procedure per year of scraping out the tumors in the bladder and an estimated over 2.5 million instillations of various drugs, mitomycin, BCG, Interferon, et cetera, for this disease.

So why do we need new treatments? Well, for the intermediate risk patients, it's certainly the case that neither BCG nor mitomycin C provide reliable long-term disease relapse rates.

The same problem is that for high risk, but in the high risk, we have even less options. All we have is BCG or we have the removal of the bladder which is not a very acceptable option. What about the patients that can't get BCG because they have immune related issues or they develop intolerance or significant side effects? We really don't have anything to offer this.

And just as a personal note, I've been dealing with patients with bladder cancer for over 15

years. I have, you know, talked with them. I've given lectures all over the country, talked with the patients and the physicians. There's a real need there for some alternatives for some advancement. There have been no significant improvement in bladder cancer treatment in the United States since the approval of BCG in the early 1990s. And we've got this disease, we've got a high prevalence. We have patients still suffering from this.

I also can tell you that I've been looking at the Synergo program for over 10 years, when I was originally asked to do so as part of a due diligence from a different company that was investigating whether they should invest in this group. I've stayed in contact. I have reviewed the papers for the journals. I've seen their presentations at the AUA. What really impresses me is that you get consistency and the efficacy of the safety for this device. I talked with the -- investigators. I've been to Milan. I've seen the patients being treated. I've talked with the patients, and it's the real thing. And I hope you will stay open minded, just to hear the results that we show you today, to show you that we really need to have a new treatment for bladder cancer in the United States. Thank you.

MS. STEIN: My name is Ahava Stein, and I'm a regulatory consultant to Medical Enterprises. I do not have a financial interest in the company, and I appreciate the opportunity to address the Panel.

I'll begin with the indications for use for the Synergo Device. The Synergo hyperthermia device, in conjunction with mitomycin C is intended for use for prophylactic treatment of patients with STCCB, following endoscopic removal of Ta-T1 and G1-G3 tumors. The Synergo treatment is clinically indicated for intermediate and high-risk patients

The Synergo treatment delivers heat to the urinary bladder wall using RF energy and the Synergo hyperthermia is delivered concomitantly with cooled mitomycin C drug solution.

In this picture here, you see the Synergo catheter system inserted into the bladder. You see the catheter balloon fixating the catheter within the bladder. The thermocouples here, when deployed, extend into the bladder wall to monitor the temperatures at the bladder wall. There are an additional two thermocouples below the balloon which monitor the temperatures within the urethra. The antenna, along the catheter, emits RF energy to heat the bladder wall.

The Synergo catheter performs basically three functions. One, as I mentioned, uniform heating of the bladder wall. The thermocouples monitor the temperature of the bladder wall and circulation of the mitomycin C drug solution into and out of the bladder.

I'm going to discuss some of the preclinical testing that was conducted on the Synergo device, the catheter and the mitomycin drug. The testing with the mitomycin C drug was submitted as part of the NDAs, submitted by the drug manufacturers, Bedford Laboratories and Bristol Myers Squibb. Medical Enterprises has been granted letters of authorization from the drug manufacturers to reference the data contained in the mitomycin C NDAs.

Additionally, the company conducted their own pharmacokinetic study, that is the Paroni Study, which assessed the effective local hyperthermia on the systemic absorption of mitomycin C during a Synergo treatment. This study showed that hyperthermia caused an increase in mitomycin C penetration into the bladder wall and showed that there were higher plasma concentrations of MMC, in the group administered hyperthermia in conjunction with MMC, compared to the group receiving MMC alone.

Despite the increase in the penetration of the mitomycin C into the bladder wall and the higher concentrations of MMC, the plasma levels of MMC at twice the indicated dose, the highest MMC plasma concentration was still 6 times less than the critical toxic systemic dose that causes bone marrow suppression.

So in summary, this test demonstrates that the hyperthermia treatment enhances the mitomycin C uptake into the bladder wall, while maintaining MMC plasma concentrations that are still well below the toxic levels.

Another study that the company conducted evaluated the degradation of mitomycin C when heated. Mitomycin C was dissolved in different IV fluids including dextrose and NACL, when heated to 50 degrees, temperatures that are higher than administered during a Synergo treatment. The results demonstrated that the MMC degradents were below the Gensia Sicor specification limits for these impurities.

Testing of the Synergo device included mechanical and electrical safety testing, and electromechanical compatibility testing as well as software validation according to international

standards. All of the tests passed and the results of the tests met the requirements of these international standards.

The catheter component of the device was tested according to the ASTM standard for Foley Catheters. The materials of the catheter were tested for biocompatibility according to the ISO 10993 standard. Bench testing of the catheter included mapping of the electromagnetic field in a liquid phantom to show that there was minimal absorption of the RF energy by the liquid.

And a second bench test in a simulated tissue model demonstrated that the RF energy generated by the antenna homogeneously heated the bladder wall and then the temperature rapidly decreased over four to six millimeters across the bladder wall. This was done in a bench test and then further validated in the animal study.

The animal study was conducted to demonstrate that during normal treatment conditions, there are no risks to the bladder tissue or to the adjacent organs. The sheep model was chosen as the sheep bladder is similar to the human bladder. Temperature mapping was conducted of the internal bladder wall as well as the external bladder wall and

the adjacent organs during a Synergo treatment.

At the end of the study, the animals were sacrificed and pathological evaluation of the bladder organs, the bladder tissue and the adjacent organs were compared to control animals.

The results of the animal study demonstrated that the Synergo thermocouples temperature measurements were accurate when compared to independent temperature monitoring system. The results of the study also demonstrated that the temperature was homogeneous over the bladder wall and decreased by a magnitude of three to five degrees over the bladder wall, internal to the external bladder wall, and a temperature drop of five to seven degrees was measure at the adjacent organs.

And finally, the animal study demonstrated that there were not risks of irreversible damage to the bladder or to the adjacent organs at temperatures that were higher than administered during a normal Synergo treatment.

I will turn this over now to Dr. Witjes for a summary of the clinical studies.

DR. WITJES: Okay. Ahava, thank you very much. Dr. Talamini, Panel members and guests, thank you very much for the opportunity to speak here about

this technology. My name is Fred Witjes. I'm a oncological urologist working in The Netherlands, and I'm involved in the treatment of bladder cancer patients, guidelines and things like that, as you can see. As such, I am already treating patients with this machine since 2001. So I have around seven years of clinical experience with this device, and I am a principal investigator of one of the studies that I will talk about, namely Study 102.1, but that will come later.

I'm very thrilled that we finally are able to present this data for the American people since I've been treating already for seven years, people in Europe with the device, and I'm very impressed by the results we've had so far and hope we can achieve similar results in American patients.

These will be the studies that I will be shortly addressing. The first 101 and 102 are randomized controlled trials which will be used for safety and efficacy. Then we have the European prophylactic patients group which is an uncontrolled commercial use dataset which we also will be using for safety and efficacy. And then you can see that there are three smaller trials, that are listed below, uncontrolled and one controlled study which we

will only use for safety data.

I'll first start, of course, with pivotal study, the 101.1. The objectives of the study were to compare safety and efficacy of the Synergo hyperthermia versus mitomycin C alone for prophylactic treatment of superficial bladder cancer.

The primary endpoint was the comparison of the recurrence rate at two years. You've heard from Professor O'Donnell that this is a very common and also very logic endpoint for superficial bladder cancer trials.

Secondary endpoints obviously were comparison of progression, stage and grade, comparison of the occurrence of CIS, comparison of the occurrence of upper urinary tract tumors or tumors in the prostatic urethra, and finally comparison of the occurrence of distant metastasis.

The sample size calculation was initially based on the primary endpoint of the two-year recurrence rate. The initial assumptions for calculation were a 2 year recurrence rate in the mitomycin C only group, the control group of 40 percent based on the scientific literature of the '90s. The study was designed to detect a 50 percent reduction in this recurrence rate in the Synergo

group versus the mitomycin C control group with a power of 80 percent and a 5 percent level of significance. So the initial sample size calculation case up with 158 patients.

The protocol did call for interim analysis when 80 patients completed the one-year follow-up. It was done a little bit earlier than planned due to ethical reasons, and you can see why, because the interim analysis clearly showed a major difference between the recurrence rate in the Synergo which was 11 percent versus the recurrence rate in the mitomycin C which was 62 percent. That resulted in a recalculated sample size which was now 84.

One of the things we have to address is there have been some randomization errors in this 101.1 study. Five pairs of administrative randomization errors were done at the central randomization office. The clinical sites nor the sponsor were aware of these errors until years after the trial had closed. The total number of patients in each group obviously remains unchanged because they were paired randomization errors, and realizing that there have been some randomization errors, we reanalyzed the study. We have not only looked at how they were treated but also we looked at the results

as they were randomized and then still you see that there was a significant advantage for the Synergo treatment in this case, smaller than 0.01.

There were some protocol deviations and withdrawals from the study. We had five Synergo patients withdrawn from the study. Three withdrew consent prior to receiving any treatment. For example, one patient from Sicily who lived too far from the hospital. One physician withdrew the patient from treatment due to deteriorating health before starting treatment, and we have one patient in the Synergo group with skin allergic to mitomycin C. That is one of the things that does happen, and you can also see that in the mitomycin C group, there's one patient with skin allergy. Two additional Synergo patients were not included in the Per Protocol cohort due to major protocol deviations.

This results in the following table. You see that the top line is all study patients randomized as treated. It's 42 in Synergo arm and 41 in the mitomycin C arm.

The second line shows you the randomization as intended. So that means that some of the patients who did receive Synergo treatment were put in the mitomycin C arm and the other way around. That

results in 36 patients in the Synergo arm and 41 in the mitomycin C arm.

And the third line shows you randomized as treated, and again you have 37 in the Synergo arm and 40 in the mitomycin C arm.

In the second and third column you see that you missed sort of one patient, but one patient who had a randomization error also had an allergy to mitomycin C. So that's why you skipped in this small table and that small table.

After two protocol deviations, you are left with the protocol analysis which has 35 patients in the Synergo arm and 40 patients in the mitomycin C arm.

What did we do after randomization? Patients were randomized for Synergo or mitomycin C therapy which is 2 times 20 milligrams. We had eight weekly sessions and after that, four monthly treatment sessions. Follow-up was as stated, two years, and we did that every three months in the first two years. And the endpoint assessment was a histologically proven, biopsy proven tumor recurrence. So not only by visual cystoscopy but biopsy proven.

Here you can see the three centers which

have been doing this trial. They are, of course, -- centers, one from Milan, one from Palermo and one from Israel.

The clinical data of the study, we have been monitoring them and 100 percent of those CRFs according to the GCP requirements that was performed. There was a FDA audit in 2005 of all the sites that were in this study and they confirmed that the CRFs were an adequate reflection of source documentation. So we think that safety and efficacy data are adequately captured on CRFs. Since we did retrospective until '97 and prospective after '97, we compared those two datasets, and we see that there is a consistent reporting of the adverse events throughout the study. So even before and after 1997.

Here you see the baseline characteristics of our patients. You can see that they are well balanced between the two Synergo groups, and despite of the facts that we have for sample patients with -- result, for example patients with the -- and for example also patients with -- lung tumors, according to the EAU risk criteria, none of those patients was in the low risk category, half of them approximately in the intermediate risk category and half of them approximately in the high-risk category.

Blinding has been an issue. Well, as Professor O'Donnell already told you, investigator blinding is not typically performed or actually not performed at all in intravesical therapy trials published in scientific literature. As Chairman of the Non-Muscle Invasive Bladder Cancer Group, we've done many trials in the -- to see. We've never done on with blinding. The pivotal study submitted to the FDA, for FDA approval also, were not blinded, for example, the BCG trial or the Valrubicin trial.

Moreover, it's very difficult to blind for Synergo treatment because patients are obviously aware of the treatment they get. They feel the heat during the treatment and also the urologist who checks the patient is obviously aware of the treatment that the patient had because of the thermal effects that you see during cystoscopy.

Moreover, the long-term results of this trial, the Synergo trial, actually confirm that the study results that we have, for example, after two years were not biased, but they are absolutely consistent.

If you look at the efficacy results, you see here three scenarios. The first line is evaluated as treated. You see that the scenario

group has a two-year recurrence rate of approximately 19 percent versus 62 in the mitomycin C arm, obviously statistically very significant.

Then we also looked, of course, at randomized as intent so as they should have been treated. That means that some of the patients who had Synergo therapy had a low recurrence rate versus skipped through the mitomycin C arm and the other way around. That obviously results in a little bit higher recurrence rate in the Synergo arm, 25 percent and a little bit lower recurrence in the mitomycin C arm, 55 percent, but still this is significant and the protocol analysis also again shows you a very significant advantage for the Synergo arm, around 17 percent versus 62 percent.

So Synergo treatment was consistently significantly better than the mitomycin C in all these patient analysis or patient populations.

Here you see the Kaplan-Meier curve for the treatment as randomization is treated. You see that again after approximately two years there is a sort of leveling out of the results in the Synergo group and that there's a constant drop in the patients who do not have recurrence in the mitomycin C group, and you see the final difference. This is up until two

and a half years is very clear and statistically significant.

Here you have a similar curve for randomized testing as intended. You see that the difference is a little bit less, but still there is a very large difference between the two treatment groups.

And finally you have here the evaluation per protocol again showing you a highly statistically significant and clinically relevant advantage for the Synergo treatment.

We also tried to come up with the worst-case scenario. For both of these worst-case scenarios we assumed that the one patient that dropped out of the mitomycin C group would have been recurrence free at two years which, of course, might be possible. And we also assumed that the five patients that had Synergo treatment would have had disease recurrence at first follow-up. Of course, it's not very realistic but it was the worst-case scenario we could think of and even then you see that in the scenario group, the recurrence rate is around 31 percent and the mitomycin C group is around 60 percent and that remains only clinically relevant but also statistically significant.

If you then also like the FDA has done reversed the treatments, so again put the mitomycin C treated patients in the Synergo group and the other way around, due to the randomization errors, you still see that there is an advantage with the Synergo treatment, but then the statistical significance is lost. However, I think this is not a very realistic scenario.

We had some secondary endpoint analysis, and they didn't really reveal any difference. There was no progression in tumor stage or grade. There was no occurrence of CIS in the Synergo group. No patients had carcinoma in the upper urinary tract or the urethra in the Synergo group, and no patients had occurrence of distant metastasis in the Synergo group nor in the mitomycin C group.

However, if we look at longer-term follow-up because this predominantly looks at the first two years, in the long-term follow-up, we had three patients who had distant metastasis in the control group.

Here you see the long-term efficacy analysis. You see that it goes beyond 12 years and actually just like at the beginning of the curve, you see that there is a consistent difference between the

two treatment arms in favor of the Synergo treatment. You'll see here a 10 year recurrence rate of 48 percent in the Synergo group and 10 year recurrence rate of 85 percent in the mitomycin C group. Again illustrating by the way, that it is a very nasty disease in patients and tends to come back very often.

Long-term follow-up also shows some results with regard to overall mortality or radical cystectomy, two in the Synergo group and five in the mitomycin C group. Overall mortality five in the Synergo group, nine in the mitomycin C group. None were treatment related. None were disease related.

We did a subgroup analysis with regard to some of potential significant predictive factors. You can see the list there. There was no significant effect of any of those listed there like H gender, number of previous occurrences, et cetera, et cetera, of the efficacy analysis. However, we did find significant effect of the history of recurrence. So the first episode, recurrent, first is recurrent to a high recurrence and also of the EAU risk category, which is not surprising because in the EAU risk category, one of the very important things is this history of recurrence, and you'll see that even if

you adjust for these prognostic factors, that the Synergo treatment remains better than the mitomycin C group, giving the impression that the results are a little bit more outspoken if you use that in higher risk patients.

The next thing after talking about the results is talking about the side effects. You see here that many of the side effects, there was no statistically significant difference. Like for the dysuria, hematuria, tissue reaction, urethral stenosis and skin allergy, urethra urinary tract infection and bladder wall necrosis, two were in favor of mitomycin C only which was pain and posterior wall tissue reaction. The ones highlighted in yellow, I will discuss in one of the next slides.

Other adverse events are very seldom. You'll see, for example, anxiety, amnesia, and then hypertonic bladder which has been noted in one patient each in the Synergo group and fever and urgency, general weakness and the false passage which is only again noted in one patient, so that it is not significantly different, and reduced bladder capacity was also not very oftenly seen, but I will also address it in one of the next slides.

With regard to pain, we included all forms

of pain being bladder spasms, intolerability to the treatment, pain in general and urethral pain. This only happened actually in a small number of patients resulting in shortening of treatment, 10 out of 425, or skipping the treatment for one week, delay of one week of treatment due to pain which was 7 out of 425. All these patients, all these pain problems, and I recognize that from my own patient population, is actually mild. It's easily manageable with medication, and it is transient.

Posterior wall tissue reaction is typically something that is caused by the hyperthermia. It is asymptomatic, and you detect it only at the follow-up cystoscopy. We made a visual scoring system which was mild, moderate or severe, mild meaning some redness, moderate meaning some mucosal damage and severe you also see some necrosis. The severity was not related to symptomatic yes or no. We had, fore example, 10 percent of severe reactions but they were still asymptomatic.

As I told you, these were resolved with out medical intervention. It is, of course, due to the radio frequency antenna which is in the bladder. It is superficial. You don't see any involvement of the muscle, and it actually gives minor or no residual

effect. Sometimes you see some scars like you see after TUR or you'll see some residual hyperemia.

Some other adverse events which were not significantly different between the two groups, but might be important to address is reduced bladder capacity. We had two patients in the Synergo group who had reduction up until 250 and 330 MLH. So it's not a shrunken bladder but there is some reduction in bladder capacity which is actually, of course, known to be a problem after any kind of intravesical therapy.

We had some patients with urethral stenosis and stricture. Again also our urologists recognized that. That is something that you do see in patients which are treated for superficial bladder cancer because of their multiple catheterizations, multiple TURs and, of course, multiple cystoscopy procedures. The fact that the catheter we use for Synergo is a little bit larger, 20 French, than you normally use, 14 French, of course, will identify less significant stenosis in the urethra earlier. And finally dysuria which we found in some of the patients. The majority of those patients did not require any treatment and none of the patients had shortening or delay of one of the treatments due to dysuria.

We have some serious adverse events in Synergo group of bronchial bleeding, suspected MI and nephrolithiasis. None of those were related to the treatment, and also in the mitomycin C group, we had one patient with hydronephrosis, one cerebrovascular accident and one patient with leukemia, again not to be considered to be treatment related.

So to conclude the 101.1 study, I think with regard to the efficacy, I hope I have shown to you that there is a highly significant reduction in the two-year recurrence rate in Synergo group, which to my opinion also is clinically very relevant for these patients. There are compelling study results even with relatively small sample size, and that the results over time have shown to be durable.

Safety, Synergo is absolutely well tolerated and the toxicity is comparable to the literature with the wide ranges that Dr. O'Donnell has shown to you with the wide ranges for intravesical therapy.

The first supportive trial is the 102.1 study which is Synergo versus BCG. This is a randomized controlled trial, comparing Synergo treatment to BCG immunotherapy, again for the prophylactic treatment of patients with intermediate

or high-risk papillary superficial bladder carcinoma. It is anticipated to end around 2013, and we will use it as supportive data. So not to statistically compare the study endpoints but we will try to demonstrate the consistency of the results for the Synergo treatment in this other randomized controlled clinical trial.

Primary endpoint was also a comparison of the two-year recurrence rate between the two groups, same as in the 101. Secondary endpoints obviously also again were comparison of the progression rate to state higher than T1 or comparison of metastatic disease. And then an additional endpoint obviously also was the local and systemic adverse events.

The treatment was a little bit different from the treatment in the 101. The reason for that was that we use in Europe the -- schedule for BCG meaning 6 initial weekly instillations followed by 3 instillations at months 3, 6 and 12, and we came up with the Synergo treatment which was more or less the same, being 6 initial weekly instillations and then 6 monthly instillations. As you might remember in 101, we had eight weekly instillations and four monthly instillations, small difference. Follow-up again was every three months for two years, and then endpoint

assessment again was biopsy or histologically proven tumor recurrence.

The population that we are talking about is 104 patients for toxicity and evaluable for efficacy, it's 92 patients, and you can see that there are well balanced between the two treatment groups.

The baseline characteristics just like in the 101 trial are actually nicely comparable between the two study arms. You can see here all the potential baseline characteristics that you can think of. They are obviously the same in all kinds of these trials. Here you see the Kaplan-Meier curves for the time to recurrence, and you'll see again, if you look at the approximately two-year endpoint, that it is around 17 percent for Synergo which is very, very close to the results in the 101, and it is 32 percent in the BCG arm.

Secondary endpoints, we didn't have any progression in tumor stage or grade in Synergo treated patients. Of course, this is an interim analysis and based on a limited follow-up.

Here you see the side effects that did significantly differ between the two study arms. In the upper part of the graph, you'll see in red the results or the adverse events that were more common,

statistically more common in the BCG arm. As you might expect, things like fever, arthralgia, fatigue and in the lower part of the graph you'll see those results, those side effects that were statistically significantly more common in the hyperthermia group, such as obviously pain during treatment and the posterior wall tissue reaction.

And then there were some other side effects that did not differ between the two groups. So they were similar in the BCG and the Synergo groups, and I will not burden you with all these. You can read what the results are.

There were some serious adverse events. We had the urethral stricture in the Synergo group. One patient had a contracted bladder in that Synergo group. Professor O'Donnell showed you that that is on average around 5 percent with mitomycin C treatment. We had one in this study, although he was recurrent free. So his cancer obviously was cured. We had one patient with urethral bleeding with withdraw consent, and one patient with dysuria, urinary urgency and fever which was by the way transient and he went on with his therapy.

We had two serious adverse events in the BCG treatment arm. One patient with macrohematuria

and the clot retention which was treated with a catheter and antibiotics and resolved. One patient with fever, conjunctivitis and urinary tract infection, again resolved after antibiotic treatment.

So the safety conclusions for 102 are again that the expected adverse events are similar as in the study of 101.1, like dysuria, hematuria, tissue reaction, urinary tract infection, pain, posterior wall tissue reaction and bladder wall necrosis and the other adverse events are also similar in nature to the Study 101.1. And in all, I think the Synergo treatment currently is very well tolerated.

We combined these two studies with regard to some of the results we have. We are talking then about 93 Synergo treated patients at 12 unique sites, 3 sites in Study 101, 10 sites in Study 102. So one site is entering patients in both studies. And we see that there was a consistent two-year recurrence rate, consistent results across sites and consistent safety profile.

Here you see a summary of the results. You see the two-year recurrence rate in the Synergo group from the 101 study which is 19 percent. It is 17 percent in the 102 study. So with a similar patient profile, it is very close to each other. We see a 63

percent recurrence rate in the mitomycin C group. That is a little bit higher than you see from the meta-analysis from literature. That's 42 percent but obviously in the meta-analysis also, low risk patients have been included and in the Study 101, we only included intermediate to high-risk patients.

If you look at the BCG results, they're very nicely comparable to the literature, 32 percent recurrence rate in our study as compared to 35 in the literature and obviously in the literature, you only treat intermediate and high-risk patients with BCG. So that's why you don't find the difference that we find in the mitomycin C treatment.

Then shortly, some of the supportive trials. The European Prophylactic Patient Trial, it's a single-arm trial, it's uncontrolled, and it's for commercial use of the Synergo device. The patient selection, treatment sessions and follow-up examinations are actually similar to the two studies I already discussed. You'll see that it is, for example, similar amount of high-risk patients, that is 58 percent in the European Prophylactic Patient Study, 55 in the 101 and also 55 in the 102, and we are now talking about 186, it says here 68, but I'm sorry for the mistake. It's 186 patients with close

to 1600 Synergo treatments.

We have a little bit higher recurrence rate in this EPP results. The reason for that is that although we have a similar amount of high-risk patients, we have more patients with highly recurring tumors in these EPP dataset. It is 60 percent in the EPP with highly recurrent tumors as opposed to 36 percent in the 101 and 22 in the 102. And highly recurrent is defined as at least three recurrences in the last two years. And you know from one of my previous slides that that was one of the most important prognostic factors. So we come up with a 32.2 percent estimated recurrence rate at two years, which is still far better than mitomycin C and at least comparable to BCG treatment.

We have a group of patients who have had bladder salvage treatment, as those are patients again extremely high-risk patients, also at least 3 recurrences within the last 24 months, but also patients who failed prior BCG treatments, and actually they were candidates for cystectomy. It's a group of 82 patients with over 800 Synergo treatments, and we will present this only for safety.

The next supportive trial is the 101.4. This is an older study from the nineties, controlled,

monitored, one arm clinical study. It's ablative indication for the use of patients with transitional cell carcinoma of the bladder. So patients for whom TUR was not possible or was not recommended, for example, very old patients, this is a dataset of 42 patients with close to 400 Synergo treatments, and we will use these data for safety.

And a similar group of patients is the European Ablation Patients -- which is after this 101.4 study. We went on with treating patients with ablative intent. So again ablative indication for the use of the Synergo machine, patients in whom the TUR was not possible or not recommended. That's a relatively large group of patients, 104, with close to 800 Synergo treatments and again these patients are presented for safety.

And if you look at these supportive studies, the EPP, the Bladder Salvage group, the 101.4 and the European Ablation group of patients, we see that again the expected adverse events are quite similar to the ones reported in the 101.1 and 102.1 and also adverse events were similar to these two studies, and that there were no serious adverse events related to the Synergo device.

Having said this, I hope I've convinced you

or I've shown you that the Synergo treatment is absolutely clinically very effective, not only significantly better but also clinically very relevant, and that the side effects are very manageable, limited and usually self-limiting, and at least in the same range as we see for other intravesical treatments, and I hope that American patients in the future will have some advantage of this treatment. Thank you very much.

DR. GROSSMAN: I'm Barton Grossman, and I am a consultant to Medical Enterprises. I have no equity interest in this company.

The treatment of intermediate and high-risk bladder cancer continues to be a significant problem in the United States, and personally from my practice, which is about 90 percent related to bladder cancer. Both mitomycin C and BCG are recommended by the American Urologic Association and are commonly used for the treatment of these diseases.

BCG is characterized by high initial efficacy, but there is a significant deterioration in the proportion of patients that remain disease free over time. This continues to be a serious problem.

Furthermore, BCG has significant local and

systemic toxicity, and this is an ongoing problem, and I continue to see patients referred to me with serious systemic toxicity from BCG.

There is a need for more effective and less toxic treatment particularly for intermediate and high-risk bladder cancer.

There are safety data on over 4,500 Synergo treatment sessions in 506 patients. Similar toxicities have been reported in the pivotal study and across all five supportive clinical studies.

The most common toxicity is that of posterior wall tissue reaction and pain due to the hypothermia. Importantly, the posterior wall tissue reaction was found only at surveillance cystoscopy. These patients were completely asymptomatic. If a cystoscopy was not performed, patients wouldn't even know they had these lesions in their bladder. They resolve spontaneously. These lesions have also been seen, non-healing ulcers have also been seen with intravesical mitomycin C without hyperthermia, and I regularly see patients like this in my own practice who receive intravesical mitomycin C, and again they're asymptomatic, self-limited and usually resolve over time without specific therapy.

Pain was seen in these patients. The

proportion of patients who actually had pain is much greater than the number of sessions which involved pain. Only 4 percent of the Synergo treatments were shortened or skipped due to transient pain during the session, and again it's important to realize that when sessions were stopped, that did not necessarily prohibit future successful treatments with Synergo.

The adverse events that have been observed in the Synergo studies commonly occur with other forms of intravesical chemotherapy and intravesical immunotherapy. There very few serious adverse events that were treatment related, and overall the Synergo therapy was well tolerated.

In the pivotal trial, Study 101.1, considering the evaluable patients, randomized as treated, there was an 80 percent reduction in the rate of recurrence with Synergo compared to controls with a hazard ratio of 0.23.

Again, importantly Synergo treatment was consistently better than mitomycin in all patient analyses.

This is the data for the 101.1 and 102.1 Synergo treatment arms, and you can see that the two arms is the pivotal trial. This is the 102.1 trial. The two arms did quite well and the curves are, in

fact, very, very similar.

If we compare that with the BCG, it demonstrates the Synergo appears to be at least as good as BCG and much better than the mitomycin C in the control arm.

How does this compare with the overall experience of BCG and mitomycin C because there is considerable literature about that. If you look at BCG in the literature, the results with 102.1 are, in fact, very similar to what you could expect from previously reported studies.

Mitomycin overall, as reported, appears somewhat better than the 101.1 arm but that includes low risk patients as well as intermediate and high-risk patients. If you censor the low risk patients and you just look at the literature for the intermediate and high-risk patients, you find out again the results that were attained in the pivotal trial were very similar to what you could expect from previously reported studies.

Long-term data has demonstrated the durability of these responses, and you can see both at 5 and 10 years, Synergo is much better than mitomycin. This data is also important because it demonstrates that there was no bias in the initial

early reports of efficacy.

The regulatory standard for valid scientific evidence includes adequate and controlled investigations, partially controlled studies, studies without matched controls and well documented case histories. Furthermore, significant human experience with a market device is considered valid scientific evidence.

We do have valid scientific evidence. The pivotal trial, 101.1, Synergo versus BCG, 102.1 and the Ablation Study, 101.4, were adequate and controlled investigations. The European Prophylactic Patients, the Bladder Salvage Patients and the European Ablation Patients involved significant human experience with a marketed device.

The three trials for efficacy involved high-risk patients. More than 52 percent of these patients enrolled in the Synergo arm were high-risk, a very at risk population, and the total number of these studies, these are patients that only received Synergo was 201 patients, a significant group. The safety, listed here, involves a total of 506 patients.

Synergo treatment was demonstrated in the pivotal trial to be much better than mitomycin C, for

the prophylactic treatment of intermediate and high-risk non-muscle invasive bladder cancer. The data suggested that Synergo may be comparable if not better than BCG. Synergo has low, acceptable and predictable toxicity, without the potential life threatening adverse events that have ultimately been reported with BCG but still occur on a regular basis throughout the United States.

Patients treated with Synergo are virtually identical to the intermediate and high-risk patients in the United States, and I must say in my patient population.

The pivotal trial results are compelling and furthermore, they're consistent across studies. The long-term results show that there was no assessment bias. Synergo therapy fills an important need for treatment of intermediate and high-risk patients in the United States. The pivotal study, 101.1 and the supportive data, provide reasonable assurance of safety and effectiveness based on valid scientific evidence.

I've had the opportunity of seeing Synergo therapy. It's amazingly easy to give. It is very well tolerated. I've reviewed the data and am very impressed with the results. I hope you also agree

that this is an important new therapy which is safe, effective and needed for our patients in the United States.

DR. O'DONNELL: Thank you. I'll conclude with a discussion about the post-approval study, and I'd first like to begin by emphasizing that the sponsor is committed to documenting the consistency of the Synergo device in the treatment of the U.S. patient population and update the labeling to accurately reflect its performance and precautions for its use in the U.S.

And while we strongly believe that the data that we've presented so far, showing the efficacy and safety, is compelling, we realize that it's important that for the U.S. population to see the device in use and to have data from our own patients. In fact, it would be a poor marketing strategy to attempt even to bring a new therapy into the U.S. without any U.S. experience and try to sell it to the U.S. population. So it's understood that even if the panel were to say we don't need a post-approval study, we would strongly do this as a company. I say we. I would support, the sponsor would support this as a company for bringing this experience into the U.S. to provide exactly the type of information that we heard about

in the previous lecture about how it performs in the subgroup of populations, that demonstrate that the toxicity profile is consistent in our group of patient as well.

So with that in mind, I'm going to give you just some brief ideas of where we put the post-approval study design with the caveat that the company remains flexible and open to further input from the Panel, from the FDA, to make this the best study to provide the benefit for the patients and for the physicians in the U.S.

So we would begin with the major objective being to demonstrate and to substantiate the safety of this Synergo system in the U.S., and for this, we feel that a single-arm study would be the appropriate study group to use. We would use the treatment regime as demonstrated in the pivotal trial, namely eight weekly sessions with four monthly maintenance sessions. With a follow-up program that conforms to the standard of care in the United States, essentially every three months cystoscopy for the first year, to obtain certainly all the safety data but also to record and to provide the data for the recurrence rate including the results from cystoscopy, cytology and biopsies as appropriate.

The key eligibility criteria would be those that have been used already in the studies that have been mentioned, namely restricting this to stage Ta and T1, grade 1 through grade 3 bladder cancer, superficial bladder cancers that conform to the intermediate and high-risk categories in the EAU definition. And in all cases, complete eradication of the tumors attempted ahead of time with the transurethral resection.

The key exclusion criteria will remain not to treat patients in the low risk group with a single, low grade papillary tumors, not to treat patients with muscle invasive disease, anything above stage T1, and not to treat patients with carcinoma in situ, CIS or Tis.

The appropriate endpoints certainly for the safety would include those that have come out through the previous safety studies, to indicate these are the events that we would expect to see with the Synergo treatment including, of course, the posterior wall tissue reaction, pain, dysuria including other urinary tract symptoms as frequency and urgency, the incidence of stenosis and stricture, hematuria, false passage, hypotonic bladders, reduced bladder capacity, bladder contracture, urinary tract

infection and bladder wall necrosis, but certainly also to include any other adverse events that would emerge during this kind of post-approval analysis and data collection.

I wish to apologize in advance to the FDA that we originally put together a post-approval study. It wasn't clear to us all the details of what a post-approval study would be. We have evolving thoughts on the subject and came to realize that the original idea of putting together a non-inferiority trial based on the set points for the eight different adverse events occurring in the 101 and 102 study was really unrealistic, unworkable, and didn't conform to the spirit of what a post-approval study really is meant to do. So that is not a clinical meaningful post-approval study, and we really don't feel that this is the appropriate kind of study that we should do, and so we withdraw that formal study concept from the field.

What we now feel is more appropriate is a representative group from the U.S. populations, that include at least about 120 subjects that would represent a similar amount that you saw on the combined 101 and 102 studies. It would represent about a quarter more patients, about 20, 25 percent

more patients from the cumulative experience for the safety and about another 50 percent increase in the number that we already have for efficacy, and would involve about 5 to 10 U.S. sites.

The type of analysis would be more descriptive certainly of the adverse events, the adverse event rate per treatment session and per patient, and would provide point estimates at 95 percent confidence intervals to be reported to be used to update the labeling so that we have a label that actually reflects and confirms what we've already seen in the European studies.

This would include as well a training program. In fact, as you can imagine, we've seen a lot of new technology come through in urology. We began really first with extra corporeal shock wave lithotripsy. It's evolved into microwave hyperthermia for BPH, green light lasers, cryosurgery. You know, urologists are a group that tends to embrace new technology but with that comes the incumbent need to have a training program to make sure that physicians and their staff are properly educated in the use. And so the company feels that this is an important part of this process as well which would include a training program with didactic

elements, a written set of format for teaching and videos, a mentorship by physicians that are experienced with the technique, to come and train physicians and technical staff including on-site training and then, of course, an assessment of proficiency.

So I want to thank you, the entire Panel and the public and FDA, for being open minded to listen to this, about Synergo, which we feel is really a novel, advanced and very efficient and new breakthrough for bladder cancer. I hope you'll conclude positively with us. Thank you.

DR. TALAMINI: I want to thank the sponsor for their presentation and their punctuality. We're right on time.

It's now time for the panel to ask questions. For the Panel, please remember that you may also ask the sponsor questions during the Panel deliberations later on today. So if anyone on the Panel has an extensive question for the sponsor, it would be good to ask that now so that the sponsor would have time to prepare an answer for later today.

In addition, it would be important to ask clarifying questions at this time regarding the sponsor's presentation.

So with that, I'll ask the Panel if there are questions, and please indicate your desire to ask a question by raising your hand. Yeah, Dr. Connor.

DR. CONNOR: My, I think my first question would ask if you could describe a little bit more. I understand how we design trials and we put a great deal of thought into designing trials, but then when trials are implemented, the people at the sites don't do exactly what we hope they'd do. So I'd like to understand more on your first trial about how the randomizations just didn't work out the way you thought. I think there were at least five patients who randomizations got switched on and can someone speak to how exactly that happened. I'd just like to understand that better, why it occurred so often.

DR. TALAMINI: And I would ask the sponsor in your response, if it appears that there needs to be an extended response, let us know so we might do that this afternoon. We only have 15 minutes for this question and answer session.

MS. STEIN: Okay. The randomization errors occurred at the site due to administrative/clerical errors when the envelopes were pulled. The randomization forms came in and the envelopes were pulled. These were only discovered years later when

the FDA had asked us to send in the randomization scheme. We pulled the randomization scheme from the files and were reviewing it before we gave it to the FDA, that's when these randomization errors were discovered. So they were really discovered long after the study was completed. The clinical sites were unaware of it. The sponsor was unaware of these randomization errors until much later. We had mentioned that the numbers were, they were switched in pairs. So both study groups ended up with the same number of patients at the end and I think most importantly is that the statistical analysis that was at the end, where we took that into consideration, and we did a worst-case scenario analysis, we still found that there was a statistical significant between the groups.

DR. TALAMINI: Dr. Connor, further questions.

DR. CONNOR: So I think I'm still not clear how this mixing up, especially since it sounded like it was one to one, where a patient was randomized to Synergo versus the other treatment, were individually switched. It wasn't someone was randomized to something and got the other treatment. It was that this mixing or, you know, mismatching occurred which

I don't understand.

DR. O'DONNELL: A piece of paper went to the wrong -- got switched between two groups of patients, between the pairs. One thing that Ahava didn't mention though that I think is important is that of the characteristics of the patients that were switched were looked to see if, well, did that result in, you know, shifting of risk groups or shifting of the higher stage tumors or something or one or the other, and they were really indistinguishable.

DR. CONNOR: And in particular, I was just wondering about age, since it looked like the age in the controlled population in that trial was higher. I wondered if there was any systemic issue of higher age patients being involved in that mismatching.

DR. O'DONNELL: That I don't know.

DR. TALAMINI: If you're not certain, we can certainly look into it.

DR. O'DONNELL: I think that whatever -- I mean obviously it was small numbers, five patients each. There was nothing that was obvious. It should be noted that 65 is close to the median point where patients present with bladder cancer. So it's relatively an arbitrary thing. We probably picked it because it's kind of a convenient Medicare related,

you know, endpoint, and it has no real clinical significant. Mitomycin C doesn't appear to have a different activity level based on age related differences.

DR. CONNOR: Okay. Thank you.

DR. TALAMINI: Other topics? Dr. Redman.

DR. REDMAN: Yeah, just on slide 37 and also 39. Was the 80 percent follow-up at one year a predetermined, a priority, that that would be the interim analysis? Usually accept events occurring for a priority analysis. That's my one question on that. And the other, why 80 -- and if that was, why 80 patients at 1 year follow-up instead of a 2 year follow-up which was a primary endpoint which I understand was not a priority.

DR. TALAMINI: And again, if the sponsor needs time to process that question, we can, you know, hold it for later this afternoon. Please just indicate if that would be favorable.

MS. DEUTSCH: I haven't been formally introduced. I'm Lisa Deutsch, a biostatistician. I took over the analysis of this project after the monitoring started, after 1997. The interim analysis was conducted by the original statistician that designed the study. It was planned that 80 patients,

that after one year follow-up but for ethical reasons, the study was stopped earlier, and there was a data monitoring committee that had decided to stop the study and provide an interim analysis and see if there was -- because they actually saw, because there was no blinding, that the Synergo patients had a very much better safety profile than, efficacy profile, survival profile than the other patients, than the mitomycin patients, and I assume that they had decided to provide the interim analysis at that time based on that information.

DR. TALAMINI: Dr. Redman.

DR. REDMAN: That's the first I've heard that there was a data monitoring committee. So was there an independent data safety monitoring committee set up at the time this trial was done or that made that decision?

MS. DEUTSCH: Yes, there was.

DR. TALAMINI: Other questions? Dr. Dahm.

DR. DAHM: I have a question with regards to the case report forms. From my reading, it's my understanding that there were in the initial phase no case report forms, and that those were instituted secondarily I be in 1997. The trial was started in 1994, and the case reports were instituted in 1997,

and then retrospectively completed. I just wanted to understand that a little better especially in the context that I think most of your events occurred in the first two years. So if the trial accrued over three years and then you went back and did the case report forms retrospectively, if that is correct, if my understanding is correct, what the potential impact of that may have been.

MS. STEIN: In 1997, that is correct. The CRFs were prepared in 1997, and the information from the patient's hospital records were transcribed from the hospital records onto the CRF. From that point on, all the patient data was prospectively completed on the CRFs as well as on the hospital source documentation. We had mentioned that there was 100 percent monitoring according to GCP requirements of all the CRFs versus hospital source documentation including those that were transcribed before 1997 and throughout the study until the end of the two-year follow-up in 2001. The FDA conducted a BIMO audit. That's a bioresearch monitoring audit by a FDA inspector in 2005 where he inspected also the CRFs versus the source documentation. As we presented in this slide, we mentioned that in his report he had written that his finding was that the data on the

CRFs were an adequate reflection of the hospital source documentation.

DR. WITJES: A small additional remark, what comes out of the results of those CRFs before '97, after '97 and in the supportive trials is similar. So we didn't find any change in reporting of, for example, adverse event because that might be one of the things that you're afraid of.

DR. TALAMINI: So let me just ask the Panel if there are other major issues that might require the sponsor to come back to us this afternoon after further analysis. If we could make sure that we get those now. Are there any Panel members that would have such a topic or issue? Dr. Redman.

DR. REDMAN: Again, just -- this is regarding supportive data. On the 5 and 10 year follow-up, do you have the number of patients that were followed for that period of time? In other words, I'm sure there are dropouts. I'm sure it wasn't 100 percent. That's just because of the supporting data that you're presenting, and also on slide 71, just for clarification, you're claiming 90 patients. I think it was 48 and 42 for an arm in support of that. Were those 90 patients followed up beyond the two years or at two years of follow-up

because I didn't count the hash marks, but it looks like a lot of patients never made it -- hadn't made it yet to that two years. So is that 90 patients that were followed at two years or beyond?

DR. TALAMINI: And again, if the sponsors require more time to answer, that's fine.

MS. DEUTSCH: I assume slide 71 refers to the 102.1 study?

DR. REDMAN: Yes.

MS. DEUTSCH: So in that case, well, that interim analysis was provided and the data lock was in 2007 and we have more follow-up to date but we're not going to look at that right now. And then the 101 study, I can tell you that in the long-term follow-up, in the mitomycin group, after 2 years, there were 11 patients that were still alive without recurrence after 23 of the patients had already had recurrence prior to the 2 years endpoint. So -- and in the Synergo, there were 28 patients that were followed up after 2 years, between the 2 and 10 year and the long-term analysis out of which 6 had already recurred prior to the 2 year endpoint if that answers your question.

DR. TALAMINI: Other --

DR. O'DONNELL: Yeah, just to clarify a

point that one reason the numbers are small in the 102 group in the long-term follow-up is that most of the patients of the mitomycin C arm recurred. So there weren't many patients at risk left to follow them for a long period of time, but the numbers were greater in the Synergo group.

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

DR. CONNOR: I think this is a brief clarifying question. It's my slide 39, but in your 101.1 study, you do this interim analysis when there were 80 patients and you said it was on the slide that you recalculated the sample size to be 84, and I wanted to clarify, I assume that there wasn't the sample size recalculation but rather by the time, you know, if someone took a dataset with 80 patients, looked at it and said, oh, there's a difference here, let's stop this trial, but by the time you stopped the trial, 4 more patients were enrolled. Is that true versus a conceivable size recalculation?

MS. DEUTSCH: I'll answer that. The interim analysis was called for when 80 patients had completed 1 year follow-up but the data safety monitoring committee alerted the company, the sponsor, to provide interim data and the study

statistician at the time provided the analysis on 39 patients who had completed a 2 year follow-up.

DR. CONNOR: And how many were in the trial at that point?

MS. DEUTSCH: There were 64 patients --

DR. CONNOR: Okay.

MS. DEUTSCH: -- in the trial at that point, and he recalculated the sample size and extended the study so that they would complete 84 patients with 2 year follow-up.

DR. CONNOR: Okay.

DR. TALAMINI: Dr. Donatucci.

DR. DONATUCCI: Yes. I would just like to understand a little bit better the -- just looking at the numbers, three centers from '94 to '99, if I understand it, and we have a breakdown in the number of patients per center, but what I don't see and don't understand is how many patients were pre-1997 when the case report forms were generated and how many were post-1997?

MS. STEIN: Approximately two-thirds of the patients were already involved in the study by 1997. That means that they were enrolled but they did not necessarily have two-year follow-up by that time.

DR. TALAMINI: Okay. I think seeing no

further questions, our schedule now provides for a 15-minute break.

I remind Panel members that there should be no discussion of the PMA during the break, amongst themselves, with the sponsor or with the public.

It is now 10:15. So we will resume promptly at 10:30. Thanks.

(Off the record.)

(On the record.)

DR. TALAMINI: It is now 10:30 by my watch. I'd like to call the meeting back to order.

We will now hear FDA's presentation. The first FDA presenter is Mr. John Baxley, the review team leader for this PMA. Mr. Baxley.

MR. BAXLEY: Good morning. I'd like to thank the Panel for your time and effort in reviewing this PMA. My name is John Baxley, and I would like to present the FDA review of the Medical Enterprises Synergo SB-TS 101.1 Device and mitomycin C.

The Synergo SB-TS 101.1 Device and mitomycin C, collectively referred to as the Synergo system, is a device/drug combination product. The lead review was conducted by the Center for Devices and Radiological Health.

As presented earlier by the sponsor, the