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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + +

October 20, 2021
9:00 a.m.

Via Zoom Videoconference

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INDEX

	PAGE
CALL TO ORDER - Frank R. Lewis, Jr., M.D., Ph.D.	8
PANEL INTRODUCTIONS	8
CONFLICT OF INTEREST STATEMENT - Candace Nalls	12
TEMPORARY VOTING MEMBER STATUS STATEMENT - Candace Nalls	14
GENERAL ANNOUNCEMENTS - Candace Nalls	15
SPONSOR PRESENTATION	
Purpose of Panel Meeting - Glenn Coleman	16
Description of SurgiMend PRS ABDM - Thomas Gilbert, Ph.D.	17
Clinical Context: Breast Reconstruction after Mastectomy in the U.S. - Robert Grant, M.D.	18
The Surgeon's Perspective - David M. Adelman, M.D., Ph.D.	20
Regulatory History - Diana Bordon, M.S., RAC	23
The MROC Study - Sandra Berriman, Ph.D.	25
SurgiMend Study Design - Sandra Berriman, Ph.D. and Chuck Davis, Ph.D.	28
Published Literature - Thomas Gilbert, Ph.D.	35
Training and Post-Approval Study - Sandra Berriman, Ph.D.	36
Benefit-Risk Assessment - Thomas Gilbert, Ph.D.	37
SPONSOR Q&A	42
FDA PRESENTATION	
Introduction and Background - S.W. Yoon, M.D.	54
SurgiMend Study Background - Felipe Aguel, Ph.D.	57
Device Description, Biocompatibility Studies and Mechanical Testing - Elda Treviño, Ph.D.	59
Clinical Study - S.W. Yoon, M.D.	61
MDR Analysis - Deborah Fellhauer, RN, BSN	64

INDEX

	PAGE
FDA PRESENTATION (cont.)	
Statistical Analysis Plan and Results - Yu Zhao, Ph.D.	66
FDA Q&A	71
OPEN PUBLIC HEARING	
Ian Saldanha, M.B.B.S., M.P.H., Ph.D.	89
Madris Kinard-Tomes, M.B.A.	92
Diana Zuckerman, Ph.D.	95
Maria Gmitro	98
Allen Gabriel, M.D., FACS	100
Steven Sigalove, M.D., FACS	102
Jesse Selber, M.D., M.P.H., MHCM, FACS	104
Marc Pearce, M.B.A.	106
SPONSOR RESPONSE TO PANEL QUESTIONS	109
FDA RESPONSE TO PANEL QUESTIONS	111
PANEL DELIBERATIONS	114
FDA QUESTIONS	
Question 1	138
Question 2	139
Question 3	141
SUMMATIONS	
Sponsor - Thomas Gilbert, Ph.D.	147
FINAL COMMENTS	
P. LaMont Bryant, Ph.D., Industry Representative	148
Natalie Compagni Portis, Psy.D., Patient Representative	148

INDEX

	PAGE
PANEL VOTE	149
ADJOURNMENT	161

M E E T I N G

(9:00 a.m.)

DR. LEWIS: I would like to call this meeting of the General and Plastic Surgery Devices Panel to order.

I'm Dr. Frank Lewis, Chairperson of the Panel. I'm a retired general and trauma surgeon, previously was an academic surgeon for most of my life, and the last 15 years of my career was executive director of the American Board of Surgery.

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 members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application for the SurgiMend PRS Acellular Bovine Dermal Matrix by Integra LifeSciences Corporation.

Before we begin, I want to ask our distinguished Committee members and FDA staff attending virtually to introduce themselves. Committee members, please turn on your video monitors if you have not already done so and unmute your phone before you speak. I will call your name and then ask that you please state your area of expertise and any relevant background information, your position, and the institution where you work and the affiliation which you hold in that institution. I'll call your names individually and we'll begin with Ann Marilyn Leitch.

Dr. Ann Marilyn Leitch, would you please introduce yourself?

DR. LEITCH: Good morning. I'm Marilyn Leitch, I'm a Professor of Surgery at UT Southwestern Medical Center in Dallas, Texas. I'm a surgical oncologist with primary specialization in the area of breast cancer and breast disease. I have a great deal of experience in the surgeries that we are discussing today, which informs my participation.

Thank you.

DR. LEWIS: Thank you.

Dr. Mary McGrath. Mary, you need to unmute yourself.

DR. McGRATH: Yes, thank you. Good morning, everyone, I'm Mary McGrath. I'm in San Francisco, California. I'm a plastic surgeon and I work at the University of California, San Francisco, where I am currently Professor of Surgery Emerita. My work in plastic surgery over the years has included many decades of being involved in breast reconstruction and other kinds of breast surgery using multimodal techniques including the ones we'll be talking about today.

DR. LEWIS: Dr. Pierre Chevray. Dr. Chevray, you've got to -- good.

DR. CHEVRAY: Yes, good morning. I am a plastic surgeon at Houston Methodist Hospital in Houston, Texas, and I've been practicing for over 20 years and perform mainly breast reconstruction surgeries.

DR. LEWIS: I don't see Dr. Hickerson on the monitor, is he available? If not, we'll go to Dr. Alan Matarasso.

DR. MATARASSO: My name is Alan Matarasso, I'm a practicing plastic surgeon in New York City. I'm in private practice and a Professor of Surgery at Hofstra Medical School. I'm the past president of the American Society of Plastic Surgeons and I have an interest in breast surgery. Thank you for having me.

DR. LEWIS: Dr. Colleen McCarthy.

DR. McCARTHY: Good morning. My name is Colleen McCarthy, I am an associate attending surgeon at Memorial Sloan Kettering Cancer Center in New York. As a reconstructive surgeon, I perform oncologic reconstruction but specialize in breast reconstructive surgeries using multimodalities.

DR. LEWIS: Thank you.

Dr. Howard Sandler.

DR. SANLDER: Thank you. I'm Howard Sandler, I'm the chair of the Department of Radiation Oncology at Cedars-Sinai in Los Angeles, and a long-time radiation oncologist.

DR. LEWIS: Dr. Karla Ballman.

DR. BALLMAN: All right. I am Karla Ballman and I am the division chief and Professor of Biostatistics at Weill Cornell Medicine in New York. My work has focused on clinical trials and observational trials and I have a lot of experience in the cancer area. Or breast cancer area.

DR. LEWIS: Thank you.

Dr. Christianne Roumie.

DR. ROUMIE: Good morning. My name is Christianne Roumie, I'm a Professor of Internal Medicine, Pediatrics, and Health Policy at Vanderbilt University Medical Center. I'm also a staff physician at the Tennessee Valley Health System, which is a VA health system. Most of my expertise is in epidemiology, particularly cardiovascular epidemiology.

DR. LEWIS: Thank you.

Dr. Ruth Parker.

DR. PARKER: Good morning. I'm Ruth Parker, I'm Professor Emerita of Medicine at Emory University. I am not a surgeon but I am married to one for 43 years, so I'm going to throw that on the table for you this morning. I'm not a plastic surgeon, a pediatric surgeon, and my area predominantly for the last three decades was really to advance health literacy, making content and processes of what we do in health and health care aligned with our patients' ability to get it, understand it, and use it. Glad to be here.

DR. LEWIS: Thank you.

Dr. LaMont Bryant.

DR. BRYANT: LaMont Bryant. I am global vice president for Johnson & Johnson's

general surgery business, Ethicon. I've been in the industry for about 20 years and have experience in general surgery, biologics, and combination products.

DR. LEWIS: Thank you.

Ms. Rachel Brummert.

MS. BRUMMERT: Hi, I'm Rachel Brummert in Charlotte, North Carolina. I'm a communications lead for the American Society of Pharmacovigilance and I'll be the Consumer Representative today.

DR. LEWIS: Thank you.

Dr. Natalie Compagni Portis.

DR. PORTIS: Good morning. I'm in the San Francisco Bay area and I'm a psychologist working primarily with patients with breast cancer and other life-threatening illness and I'm the Patient Representative today in the meeting.

DR. LEWIS: Last, Dr. Binita Ashar, who's the Director of the Office of Surgical and Infection Control Devices for the FDA.

DR. ASHAR: Good morning. Again, Binita Ashar, I'm a general surgeon by training and I have been at FDA for over 20 years and serving as the Director of the Office of Surgical and Infection Control Devices, responsible for the review and regulation of these products, and we sincerely appreciate your time this morning. Thank you so much.

DR. LEWIS: Two members of the Panel, Dr. William Hickerson and Dr. Stephen Li, have not yet joined, but we will introduce them when they do. And I thank all the rest of you.

MR. VEIZIS: I'm sorry, we still need to introduce Dr. Hoffman and Dr. Li has just joined. My apologies.

DR. LEWIS: Dr. Li, I don't see your -- are you available?

MR. VEIZIS: Definitely, Dr. Hoffman is. I think we still need to introduce him.

DR. LEWIS: Dr. Philip Hoffman, I'm sorry, I missed you.

DR. HOFFMAN: Can you hear me now?

DR. LEWIS: Yes. You're muted. Now you are. Good, now you're okay.

DR. HOFFMAN: I'm Philip Hoffman, I'm a professor at the University of Chicago, I'm a medical oncologist. Most of my practice has been involved with breast cancer over the last 40 years, actually, and perhaps relevant is that until a few months ago I was the chair of the ODAC, the Oncologic Drugs Advisory Committee to the FDA.

DR. LEWIS: Thank you.

Dr. Stephen Li, would you introduce yourself?

DR. LI: Yes, I'm Stephen Li, I'm a Ph.D. chemist. My area is biomechanics and biomaterials. I've worked in academia, industry, and had my own company for years and now I'm a private consultant.

DR. LEWIS: Thank you.

All right, we'll now move on. Ms. Candace Nalls, the Designated Federal Officer for today's devices panel, will make some introductory remarks.

Dr. Nalls, would you please proceed?

MS. NALLS: Good morning. I will now read the Conflict of Interest Statement.

The Food and Drug Administration (FDA) is convening today's meeting of the General and Plastic Surgery 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 Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Subsection

208 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. Subsection 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have 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.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal 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. Subsection 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application (PMA) for the SurgiMend PRS Acellular Bovine Dermal Matrix (SurgiMend PRS ABDM) by Integra LifeSciences Corporation. The proposed indication for use as stated in the PMA is as follows: SurgiMend PRS Acellular Bovine Dermal Matrix is intended for use as soft tissue support in post-mastectomy breast reconstruction. SurgiMend PRS Acellular Bovine Dermal Matrix is specifically indicated for immediate, two-stage, submuscular, alloplastic breast reconstruction.

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. Subsection 208.

Dr. P. LaMont Bryant is serving as the Industry Representative, acting on behalf of all related industry. Dr. Bryant is employed by Ethicon, Inc., a subsidiary of Johnson & Johnson.

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 an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

A copy of this statement will be available for review and will be included as a part of the official transcript. Thank you.

I will now read the Appointment to Temporary Voting Status Statement.

Appointment to Temporary Voting Status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as Voting Members of the General and Plastic Surgery Devices Panel for the duration of this meeting on October 20th, 2021:

Drs. Pierre M. Chevray, William L. Hickerson, Ann Marilyn Leitch, Stephen Li, Alan Matarasso, Colleen M. McCarthy, and Howard M. Sandler.

For the record, these individuals are special Government employees or regular Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

In addition, I appoint Dr. Frank R. Lewis, Jr. to act as temporary chairperson for the duration of this meeting.

For the duration of the General and Plastic Surgery Devices Panel meeting on October 20th, 2021, Drs. Philip Hoffman, Ruth Parker, and Christianne Roumie have been appointed to serve as Temporary Voting Members, and Ms. Natalie Compagni Portis has been

appointed to serve as Temporary Non-Voting Patient Representative. Ms. Compagni Portis, a patient representative, and Dr. Hoffman serve as consultants to the Oncologic Drugs Advisory Committee at the Center for Drug Evaluation and Research (CDER). Dr. Parker serves as a voting member of the Nonprescription Drugs Advisory Committee in CDER, and Dr. Roumie, a regular Government employee, serves as a voting member of the Nonprescription Drugs Advisory Committee in CDER.

These individuals are special Government employees or regular Government employees who have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

The appointments were authorized by Russell Fortney, Director, Advisory Committee Oversight and Management Staff, on September 22nd, 2021.

A copy of this statement will be available for review and will be included as part of the official transcript. Thank you.

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

Before I turn the meeting back over to Dr. Lewis, I'd like to make a few general announcements.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each time and every time that you speak.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

The press contact for today's meeting is Audra Harrison.

For the record, FDA has received one written comment. Thank you very much.

Dr. Lewis.

DR. LEWIS: We will now proceed to the Sponsor's presentation.

I want to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the request or recognition of the Chair.

The Sponsor will have 60 minutes for their presentation and may now begin.

MR. COLEMAN: Good morning, Panel members, FDA staff, ladies and gentlemen. It is a privilege to be presenting to the Panel during Breast Cancer Awareness Month. I am Glenn Coleman, the executive vice president and chief operating officer of Integra LifeSciences, a global medical technology company founded in the United States in 1989, headquartered in Princeton, New Jersey.

Today, the Panel will discuss, make recommendations, and vote on questions regarding Integra's PMA for the SurgiMend PRS Acellular Bovine Dermal Matrix. Integra is pleased to be here to present data to support the approval of SurgiMend for immediate, two-stage, submuscular, alloplastic breast reconstruction.

You will first hear from Dr. Gilbert, Tissue Technologies' vice president of research and development, who will describe the device and serve as our lead for any questions.

Dr. Grant, Professor Emeritus at Columbia University Medical Center, will then provide an overview of the landscape of breast reconstruction after mastectomy, after which Dr. Adelman, professor at MD Anderson Cancer Center in Texas, will share his experience using SurgiMend.

The very interesting regulatory history of SurgiMend will be covered by Ms. Bordon, Tissue Technologies' director of regulatory affairs.

Our medical affairs senior director, Dr. Berriman, and statistical advisor, Dr. Davis, will then present the design of the SurgiMend study and the primary clinical results that support the PMA approval. Dr. Gilbert will follow with a review of the published literature, and Dr. Berriman with our proposed training plan and proposed post-approval study. Our

detailed benefit-risk assessment and conclusion will then be presented by Dr. Gilbert.

Shown on this slide are each of our speakers. Dr. Gilbert, Ms. Bordon, and Dr. Berriman are employees of Integra. Drs. Grant, Adelman, and Davis are consultants.

And now Dr. Gilbert will provide an overview of the SurgiMend PRS ABDM.

Dr. Gilbert.

DR. GILBERT: Thank you, Glenn.

The subject of this PMA application is for SurgiMend PRS Acellular Bovine Dermal Matrix, which we will also refer to as SurgiMend or SurgiMend ABDM throughout the presentation.

SurgiMend ABDM is intended for use as soft tissue support in post-mastectomy breast reconstruction. Specifically, SurgiMend ABDM is indicated for immediate, two-stage, submuscular, alloplastic breast reconstruction.

SurgiMend ABDM is derived from fetal bovine dermis with the thickness of approximately 1 mm. The dermis is processed with chemicals to remove cellular material and to provide viral inactivation. Importantly, no preservatives or chemical cross-linking agents are used during manufacturing. The resulting product is freeze dried, cut to sizes up to 225 cm^2 in rectangular, semi-oval and slant semi-oval configurations, the photos on the right. It is fenestrated to allow for fluid egress, and terminally sterilized with ethylene oxide. Each lot undergoes in-process and finished goods testing prior to release.

The product has undergone extensive material characterization to support design verification, which includes assessment of mechanical properties, molecular integrity, and endotoxin content. A full panel of biocompatibility testing per ISO 10993 has been completed and confirmatory testing is under way to reflect the most current standards. Validation of viral inactivation has also been completed, showing greater than 6-log reduction. Mechanical and biological compatibility testing with the tissue expanders and

breast implants is under way. The testing is further supported by the totality of clinical evidence that will be a primary focus of this presentation.

At the time of clinical use, SurgiMend ABDM can be trimmed to the specific anatomy of the patient. After hydration with room-temperature saline, the device is pliable and drapable to conform to the curvature of the tissue expander, as shown in the photograph on the right. The device is designed to have sufficient suture retention strength and to provide long-term mechanical support for soft tissue surrounding the tissue expander or breast implant. The composition and structure of the fetal bovine dermis allows for cellular migration and vascular in-growth for more robust tissue integration.

I will now turn it over to Dr. Grant to provide an overview of the clinical landscape of breast reconstruction after mastectomy in the United States.

DR. GRANT: Thank you, Dr. Gilbert.

Next, I will briefly address the clinical landscape of breast reconstruction after mastectomy in the U.S. today. It is an honor to discuss this during Breast Cancer Awareness Month.

First, a bit about my background. I just became Professor of Surgery Emeritus at Columbia University. I was the plastic surgeon-in-chief at New York Presbyterian Hospital, Columbia, and Weill Cornell from 2004 until I retired this year. I have over 30 years experience as a plastic surgeon of which at least 50% of my surgical procedures were breast reconstructions. I also have over a 20-year history training surgeons and as a clinical investigator and NIH researcher.

This slide summarizes the current landscape of breast reconstruction and its role in the treatment of women with breast cancer in the U.S. today. Breast cancer is the most common cancer in U.S. women and it's expected to affect over 280,000 women this year. Breast reconstruction is a critically important option for American women post-mastectomy

because it improves a woman's body image, perception of sexuality, and self-esteem. As you know, the importance of providing women with the option of breast reconstruction after mastectomy is recognized as federal policy in the Women's Health and Cancer Rights Act of 1998.

Today there are two key approaches: autologous reconstruction that makes use of the patient's own excess tissue to recreate the breast mound, also called flap reconstruction; and alloplastic reconstruction, which is reconstruction using a permanent breast implant.

Based on current 2020 data from the American Society of Plastic Surgeons, two facts are important. Two-stage alloplastic reconstruction is currently the choice of over 83,000 women annually. This represents 60% of women undergoing breast reconstruction in the United States. And when alloplastic reconstruction is selected, acellular dermal matrix (ADM) is used in over 59,000 of these cases. The focus of today's panel is implant-based, immediate, two-stage breast reconstruction.

As shown in the illustration, SurgiMend is placed in the breast pocket during the first stage immediately after the mastectomy to create a hammock under the expander and reinforce the soft tissues at the lower pole of the breast pocket that are not covered by the pectoral muscle. Then, during post-op visits over several weeks and months, the expander device is gradually filled in volume to allow future insertion of the properly sized breast implant. After its placement in the first stage, the ADM is vascularized and integrates with the surrounding soft tissue. At the second-stage operation, the expander is removed and the permanent breast implant is placed. The ADM helps support and maintain the position of the breast implant.

In contemporary surgical practice of implant-based, immediate, two-stage breast reconstruction, there are many reasons why breast reconstruction surgeons elect to use an

ADM in this specific procedure. They include

- Patient characteristics and preference;
- Quality of the woman's soft tissues in the breast pocket and chest wall musculature;
- The planned size and weight of the breast implant to be placed;
- The surgeon's training, as well as surgical practice and standards of her or his institution; and
- The surgeon's personal accumulated experience in the practice of surgery.

In addition, in the context of FDA's 2021 safety communication regarding ADMs used in implant-based breast reconstructions, many surgeons now specifically choose SurgiMend because of its favorable safety profile.

Thank you. I will now turn it over to my colleague, Dr. David Adelman, who will present his views on the role of SurgiMend in his practice.

DR. ADELMAN: Thank you, Dr. Grant.

I'm honored to chare my personal perspective about the role of SurgiMend in my practice as a breast reconstructive surgeon. My name is David Adelman and I'm a Professor of Plastic Surgery at the MD Anderson Cancer Center in Houston, Texas. I completed my M.D./Ph.D. at the University of Chicago, my residency at NYU, a 1-year fellowship in microsurgery and complex cancer reconstruction at MD Anderson, and then joined its faculty. I've been a consultant to TEI Biosciences and now Integra LifeSciences for 10 years. In this section, I am sharing my own views as a reconstructive breast surgeon.

Patients come to MD Anderson from all over the world and it is our responsibility to provide them with state-of-the-art care. As a surgeon, I perform reconstructive procedures in all parts of the body and in patients with many types of cancer. Greater than 50% of my practice is breast reconstruction in women with cancer. The most common post-

mastectomy surgery I perform is implant-based, two-stage breast reconstruction using placement of a tissue expander followed by an implant, averaging at least 50 of these procedures a year. Today's panel discussion regarding the safety and effectiveness of SurgiMend in implant-based, two-stage breast reconstruction is therefore very important to me, as well as the one in eight U.S. women who may be affected by breast cancer.

During my 6 years of plastic surgery residency training, I witnessed a paradigm shift in breast reconstruction. Early on, post-mastectomy breast implants were only placed in a total submuscular plane that required lifting the pectoralis major, serratus anterior, and rectus abdominis muscles to provide protection and support for the implant beneath them. However, the lifting of these muscles increased patient-reported pain and muscle dysfunction, as well as decreased the aesthetics of the final breast reconstruction.

Additionally, significant operative work was needed during the planned second stage of the surgery, when the expander was removed and the implant placed, to improve the position of the implant on the chest wall, secure the lower pole of the breast reconstruction, and to improve patient outcomes.

With the advent of the first acellular dermal matrices, only the pectoralis major muscle required elevation. The ADM could replace the serratus and rectus abdominis muscles to provide the needed coverage and support of the lower pole of the implant. In my own clinical experience, women reported less pain and less muscle disuse with better aesthetic outcomes using ADMs. And by controlling the position of the tissue expander with the ADM, significantly less revision was needed at the planned second stage to achieve preferred placement of the breast implant on the chest wall. Thus, as a surgeon, I was able to offer a significant improvement in functional and aesthetic outcomes.

Although the arrival of ADMs during my residency enabled two-stage implant-based subpectoral breast reconstruction, there were still significant problems with the early use of

ADM products, including infection and poor integration with adjacent soft tissues, which all led to a high rate of reconstruction failures. Therefore, over the last decade in my career and with my background in basic science, it has been important to me and my trainees to learn about the nuances of ADMs and how they integrate with surrounding body tissues.

The data regarding SurgiMend strongly suggests a tissue regeneration mechanism that is quite different from scar formation. I now use SurgiMend regularly in my practice in two-stage subpectoral breast reconstruction to optimize the success of the reconstruction. It also facilitates the option of both subpectoral and prepectoral breast implant placement.

In addition, capturing clinical data to demonstrate the safety and effectiveness of ADMs is critically important and something we've been working on at MD Anderson. Almost a decade ago we embarked on a prospective, randomized, three-arm trial for two-stage implant-based reconstruction in women after mastectomy using either SurgiMend, AlloDerm, or no ADM at all. Ultimately, the no ADM arm had to be abandoned as patients were unwilling to be randomized to no ADM. For today's panel, this experience underscores the value and importance of the use of real-world data from the multicenter MROC study as the data platform for the SurgiMend study.

To conclude, PMA approval of SurgiMend for the proposed indication matters. The FDA's recent announcement that use of ADMs in post-mastectomy breast reconstruction is "off label" has concerned women with breast cancer. Both patients and physicians want to know and be assured that the specific ADM products are safe and effective for use in the planned breast reconstruction surgery and not being used off label.

Approval of this PMA will directly help practicing surgeons and physician educators like myself to understand the benefits, potential limitations, and nuances of using SurgiMend versus no ADM, and inform decision making with women who are undergoing mastectomy for breast cancer. It will also set the stage for future PMA-based evaluation of

other ADM products. The FDA's approval of this PMA will go a long way into making the lives of our breast cancer patients not only safer, but it will also add to our ability to restore the form and function that breast cancer has tried to take from them. I cannot think of a more appropriate time for this panel to be convened, given that October is Breast Cancer Awareness Month, and the positive impact that your deliberations will have. Thank you.

Ms. Bordon will now discuss the regulatory history for the SurgiMend product line.

MS. BORDON: Thank you, Dr. Adelman.

SurgiMend has been legally marketed and used in the United States for over 14 years since it was first cleared for sale in August of 2007, under premarket notification K071807. This device is the same product as the device that is the subject of this PMA.

SurgiMend is currently marketed with the indication for implantation to reinforce soft tissue where weakness exists, and for the surgical repair of damaged or ruptured soft tissue membranes. SurgiMend is specifically indicated for plastic and reconstruction surgery.

Since the early days of introduction, surgeons began using SurgiMend in breast reconstruction. Wishing to obtain an indication for use specific to breast reconstruction, Integra approached FDA to determine the requirements to support this labeling, at which point FDA indicated clinical data would be required.

Integra began engaging with FDA in 2015 to identify the appropriate investigational approach to study SurgiMend in breast reconstruction surgery. FDA and Integra initially considered the possibility of a randomized clinical trial. But at the time, and as continues today, ADMs were widely used in submuscular breast reconstruction surgeries and considered by many surgeons to be the standard of care. This consideration made a randomized controlled trial of SurgiMend versus no ADM unrealistic and unachievable. Given this challenge, FDA and Integra agreed that real-world evidence would be the best

approach to demonstrate safety and effectiveness. In particular, the extensive real-world data generated from the Mastectomy Reconstruction Outcomes Consortium study was identified as a source to develop real-world evidence. This study was not sponsored by Integra. Through some negotiation, it was agreed that the MROC study sponsor would provide the de-identified dataset to the FDA in a master file. Integra obtained a right of reference to analyses performed using the MROC study data. However, the MROC study sponsor did not grant Integra rights to access this dataset directly.

To address this limitation, the FDA and Integra agreed that Integra would develop a statistical analysis plan with input from the FDA, and the FDA statisticians would execute the SAP independent of Integra.

In determining the most appropriate primary endpoint to demonstrate the clinical benefit of SurgiMend in breast reconstruction, the BREAST-Q patient-reported outcome measure was identified. This was supported by the General and Plastic Surgery Devices Panel meeting held in March of 2019, during which the FDA expressed that BREAST-Q scores could be used to demonstrate ADM benefit.

In March 2020, FDA proposed the use of a single primary endpoint that addresses both effectiveness and safety. FDA and Integra agreed that the effectiveness component of the single primary endpoint would be based on the BREAST-Q Physical Well-Being (Chest) domain, and that safety would be based on the major complications in the MROC study.

Once it was agreed that this single primary endpoint could be appropriate to support a PMA, Integra developed a statistical analysis plan in collaboration with FDA. The SAP was submitted to FDA, the FDA statisticians performed the analyses and provided the results to Integra, at which point Integra began preparation of this PMA application.

As noted earlier, the SurgiMend ABDM devices proposed in the PMA application are the same devices as those cleared in the original SurgiMend premarket notification.

Although other SurgiMend configurations were available on the market during the MROC study enrollment, multiple factors support that the configurations presented in the PMA are the same configurations used in the study. Among these factors are the purchasing histories of the institutions in the MROC study, which are consistent with use of K071807 products, and the fact that the products of the original 510(k) were the only SurgiMend products designed and marketed for use in breast reconstruction during patient enrollment for the MROC study.

I'll now turn the presentation to my colleague, Dr. Sandra Berriman.

DR. BERRIMAN: Thank you, Diana.

Next, let's discuss the MROC study and why it is a relevant and reliable clinical data platform for the SurgiMend study that is the focus of today's panel meeting.

The Mastectomy Reconstruction Outcomes Consortium, or MROC, study was funded by the National Cancer Institute of the NIH and carried out over 5 years. This clinical investigation was developed by a consortium of breast reconstruction surgeons to provide objective, up-to-date information on breast reconstruction outcomes from the patient's perspective. It was carried out at 11 public and private institutions that are high-volume centers for breast reconstruction.

The MROC study recruited adult women undergoing one of eight types of breast reconstruction following mastectomy, including immediate, two-stage, submuscular, alloplastic breast reconstruction. It excluded women undergoing reconstruction following complications of breast augmentation, lift, or reduction and failed prior breast reconstruction.

The overall design and conduct of the MROC study are summarized in this slide. The MROC study was a prospective, observational cohort study. Following IRB approval and informed consent, subjects were evaluated preoperatively and at 1 week, 3 months, 1 year

and 2 years after breast reconstruction. Safety was evaluated by the capture of postoperative complications. Postoperative complications were pre-specified and identified by trained reviewers at each institution and the electronic medical record through Year 1 and Year 2 after surgery. Effectiveness was evaluated by specific patient-reported outcomes measures including the BREAST-Q, which is a validated patient-reported outcome instrument designed specifically for women undergoing breast reconstruction. These data were collected at time points referenced above.

The inclusion and exclusion criteria which are disclosed in the clinicaltrials.gov entry for this study are shown here, including the types of implant-based and autologous reconstruction procedures that were included. Note that the MROC study included women undergoing mastectomy for breast cancer, as well as mastectomy for prevention of breast cancer. The study also included women undergoing unilateral or bilateral reconstruction procedures.

Now let's consider why the MROC study provides relevant and reliable real-world data, and why the formal analysis of these data for the SurgiMend study provides real-world valid scientific evidence.

For this PMA, it is critical to appreciate that CDRH is actively relying on real-world clinical evidence for medical device regulatory decision making, including primary support for original PMA applications.

The blue CDRH publication shown on this slide provides examples of 20 PMA original applications, including surgical implants, that relied on real-world data to generate real-world evidence for premarket approval.

Not all real-world clinical data can be used to generate evidence of safety and effectiveness for regulatory decision making. The recent 2017 CDRH guidance on real-world evidence, shown on this slide, identifies the key policy issues. Real-world data must be both

relevant and reliable to provide valid scientific evidence to support the specific regulatory decision.

This slide demonstrates why the MROC study data provide relevant and real-world data that is fit for purpose for the SurgiMend PMA that the Panel is addressing today. The MROC study assesses the relevant surgical procedure: implant-based, two-stage subpectoral breast reconstruction including patient-physician shared decision making. It assesses the relevant device and control: SurgiMend versus no ADM. It incorporates relevant expert surgical technique, and the relevant diverse population of women undergoing post-mastectomy breast reconstruction. It assesses specific and relevant major complications of contemporary breast reconstruction after mastectomy, and it assesses relevant effectiveness outcomes from a woman's perspective, including the use of a validated PRO specific to breast reconstruction surgery.

This slide demonstrates why the MROC study data are reliable and that the analysis of these data in the SurgiMend study by Integra, in collaboration with the FDA, provide reliable real-world evidence.

The MROC study was conducted under the identical protocol and procedures at each participating institution, including the collection of specific data elements at pre-specified time intervals, entry and aggregation of subject data in the study's database, and quality control processes.

Data analysis for the SurgiMend study was conducted based on prospective development of the statistical analysis plan in collaboration with FDA prior to database lock and conduct of the analysis. The construct of the SurgiMend study database and conduct of the analysis were done under the FDA's stringent internal requirements for quality control and data integrity.

In summary, the MROC study data platform and the conduct of the SurgiMend study

analysis provide relevant and reliable real-world data that are valid scientific evidence for this PMA.

We'll now describe the design of the SurgiMend study. For this section, Chuck Davis will join me.

The analysis population for the SurgiMend study is the full analysis set population. It is comprised of women who enrolled in the MROC study and met the MROC study inclusion and exclusion criteria, underwent an immediate, two-stage, implant-based, subpectoral reconstruction and received either SurgiMend (the treatment group) or no ADM (the control group).

The primary endpoint (composite clinical success) is a dichotomous responder analysis developed in collaboration with the FDA. A responder is a subject who meets both of the following criteria: a score on the BREAST-Q Physical Well-Being (Chest) domain that is not more than four points lower 1 year after surgery compared with preoperative baseline score, and the absence of any of the nine major complications captured in the MROC study at 2 years after surgery or 1 year if not available at 2 years.

In the next two slides, I'll discuss each component of the primary endpoint in more detail.

The primary endpoint component of effectiveness is shown here. It is based on the patient-reported outcome of each woman on the BREAST-Q Physical Well-Being (Chest) domain. This patient-reported outcome was selected because a woman's perception of physical well-being of the chest markedly worsens after mastectomy with breast reconstruction, including immediate, two-stage, subpectoral, implant-based breast reconstruction. For this instrument, a higher score compared to preoperative baseline score shows improvement and a lower score is worse than baseline.

For this instrument, the minimal important difference, or the MID, is four points.

Therefore, at 1 year after surgery, a reduction in the score of four points or less compared with preoperative baseline score is consistent with a woman's perception of the state of well-being of the chest that she perceived prior to surgery.

The primary endpoint component of safety is shown here. It is the proportion of women with the absence of one or more of the nine postoperative major complications of breast reconstructive surgery captured in the MROC study. These nine major complications are hematoma, explantation of the breast implant, reoperation, capsular contracture, infection, dehiscence, tissue necrosis, implant rupture, and seroma.

In the MROC study, a complication is identified as an adverse postoperative surgery related event, whereas a major complication is defined as a complication requiring rehospitalization or reoperation.

For the regulatory purposes of the SurgiMend study, FDA proposed, and Integra agreed with, the use of a more inclusive definition of major complications. The definition of major complications for the SurgiMend study specifies inclusion of infection treated with oral antibiotics as a component of infection, and elective surgery as a component of reoperation.

The primary endpoint hypothesis for the SurgiMend study tests whether the proportion of women with composite clinical success (the proportion of responders) in the SurgiMend group is superior to that of the control group. The null hypothesis and the superiority hypothesis for the SurgiMend study are stated in this slide.

Because the SurgiMend study is a nonrandomized study, the test of the primary endpoint hypothesis is based on a propensity score adjustment pre-specified in the statistical analysis plan.

For the secondary endpoints of the SurgiMend study, no confirmatory testing of additional hypotheses were performed as per the statistical analysis plan.

Additional analyses of the safety data were performed. The statistical analysis plan specifies the additional safety analysis of the number and proportion of subjects in the SurgiMend group and the control group who experienced each of the MROC study complications according to the postoperative time intervals specified in the MROC study. We will discuss this analysis with the Panel today.

Treatment emergent adverse events were requested in the statistical analysis plan, but these data were not provided to Integra.

Now I'm going to ask Dr. Davis to discuss the propensity score model used in the SurgiMend study.

DR. DAVIS: Thank you, Dr. Berriman.

The MROC study was an observational study, not a randomized parallel group trial in which subjects could be randomized to one of two treatments. Because of the observational nature of the study, the statistical analysis plan specified the use of a propensity score model to adjust for baseline variables that might potentially confound the relationship between the treatment and outcome. Well-established statistical methods were used, as described in the statement shown here, from the statistical analysis plan developed in collaboration with the FDA statisticians.

This slide describes the stratification algorithm. It provides a detailed description of the technical approach involved in dividing the subjects into five categories, called strata, based on the estimated probability of each subject receiving treatment with SurgiMend. The goal was to define the strata so that within each of the five strata, the distribution of the propensity scores in the SurgiMend group would be similar to the distribution in the control group. This approach was pre-specified in the statistical analysis plan developed in collaboration with the FDA statisticians.

We will now present the results of the SurgiMend study. This slide describes the

SurgiMend study population. A total of 987 subjects were analyzed in the SurgiMend study, 119 women in the SurgiMend group and 868 women in the control (no ADM) group. The demographic, clinical, and operative characteristics, which are listed in Table 8-1 and Table 8-2 in the SurgiMend Executive Summary, were similar overall between the groups, both per subject and per breast.

As I will discuss in the next slides, after propensity analysis, the groups defined by the propensity score stratification were well balanced with respect to the selected covariates, thus approximating randomization.

As shown on this slide, the propensity score model included 21 demographic, clinical, and surgical covariates.

Next, I will present the performance of the pre-specified propensity analysis methods used in the SurgiMend study.

This figure displays the effects of the propensity score adjustment on the standardized differences between the SurgiMend group and the control no ADM group for the covariates. The red markers show the difference between the groups for each covariate before propensity adjustment. The green markers show the difference between the groups after propensity adjustment for each covariate, and are uniformly close to zero. This indicates that the propensity score model resulted in largely eliminating the impact of baseline differences between the SurgiMend group and the no ADM group.

The FDA statisticians also provided box plots showing the distribution of the propensity scores within each of the five strata. The intermediate three strata show almost identical agreement between the two groups. There is also agreement between the groups in the categories that include the smallest and largest propensity scores.

This slide shows the definition of the strata. For the pre-specified primary analyses of the SurgiMend study, the boundaries with the five propensity score strata were

determined with the purpose to explicitly include the same number of SurgiMend subjects in each of the five strata. Although this is not achievable exactly, each strata includes 23 to 24 SurgiMend subjects, as shown in column 4 of this table, which is highlighted. The boundaries of each strata are displayed in columns 2 and 3. The weights assigned to each stratum based on the number of SurgiMend subjects are shown in the right-most column, where ATT is the average treatment effect in the treated population.

Taken together, these results from the propensity score adjustment procedure demonstrate that the approach used by the FDA statisticians was successful in controlling for baseline differences between the SurgiMend group and the control group.

Dr. Berriman will now present the results of the primary analyses of the SurgiMend study.

DR. BERRIMAN: It is my honor to present the results of the primary endpoint analysis of the SurgiMend study to this Panel.

The primary endpoint analysis confirms the superiority hypothesis. A higher proportion of subjects in the SurgiMend group achieved composite clinical success compared with subjects in the control (no ADM) group at a level of statistical significance of $p = 0.02$. Specifically, the propensity score adjusted estimates show that 32.4% of SurgiMend subjects and 21.1% of control group subjects achieved composite clinical success with a difference of 11.2 percentage points. The next two slides show the results of each of the components of the composite clinical success primary endpoint.

This slide shows the proportion of subjects who achieved success regarding BREAST-Q Physical Well-Being (Chest) domain at 1 year after breast reconstruction compared with baseline. In the propensity score-adjusted estimates, the success rate was 44.5% in the SurgiMend group and 39.1% in the control (no ADM) group, with a difference of 5.4 percentage points. Directionally consistent with the composite primary endpoint

analysis, a higher proportion of subjects in the SurgiMend group achieved success than subjects in the control group.

This slide reports the proportion of subjects who experienced one or more major complications through 2 years after breast reconstruction. In the propensity score adjusted estimates, the percentage of subjects who experienced one or more major complications was 33.7% in the SurgiMend group compared with 46.7% in the control (no ADM) group, with a difference of -13.1 percentage points. Based on the boundaries of the 95% confidence intervals of the difference shown in the table, these data provide strong support for the superiority of the SurgiMend group compared with the no ADM group regarding the experience of one or more major complications.

Multiple pre-specified sensitivity and exploratory analyses were presented in the Executive Summary. In each of these pre-specified analyses, the proportion of subjects with composite clinical success is directionally higher in the SurgiMend group compared with the control (no ADM) group. This includes the propensity stratified proportion of subjects who achieved composite clinical success using an ATE-weighted analysis where ATE is the average treatment effect of the entire population and all sensitivity analyses of the primary endpoint in which modified definitions of major complications were explored.

In summary, the pre-specified primary endpoint demonstrated superiority for the SurgiMend-treated group compared with the control (no ADM) group. This result is strongly supported by the directional results in the pre-specified sensitivity and exploratory analyses.

Next, I will present the post hoc analyses conducted by the FDA.

Following submission of the PMA and public announcement of the Advisory Committee meeting, the FDA proposed the conduct of post hoc statistical analyses that were not pre-specified in the statistical analysis plan and asked Integra for approval.

Integra agreed.

The FDA statistical team conducted an analysis of the primary endpoint (composite clinical success) that was limited to the two sites in the MROC study where both SurgiMend and no ADM were used for the proposed indication. There were 119 SurgiMend subjects and 150 control (no ADM) subjects in both sites combined.

This slide shows the results of the post hoc analysis that FDA designated as the primary analysis. This analysis relies on the definition of composite clinical success, as well as the use of ATT strata and ATT weights consistent with the primary endpoint analysis in the statistical analysis plan. It shows that 32.4% of the SurgiMend subjects and 12.9% of the control (no ADM) subjects achieved composite clinical success, a difference of 19.4 percentage points. Based on the boundaries of the 95% confidence intervals of the difference shown in the table, this post hoc analysis strongly supports the findings of superiority in favor of SurgiMend in the pre-specified primary endpoint analysis.

This slide summarizes the overall results of the SurgiMend study. First, the pre-specified primary endpoint analysis based on composite clinical success addresses both effectiveness and safety. The primary endpoint analysis met the pre-specified hypothesis of the superiority of SurgiMend compared with control (no ADM) group.

Second, the multiple sensitivity and exploratory analyses pre-specified in the statistical analysis plan, as well as the post hoc analyses conducted by FDA, are directionally consistent with the primary endpoint analysis in favor of SurgiMend.

In conclusion, the results of the SurgiMend study provide strong support for the effectiveness and safety of SurgiMend in comparison with no ADM for the proposed indication.

It is now my pleasure to ask my colleague, Dr. Tom Gilbert, to present the published literature analysis in support of this PMA application.

DR. GILBERT: Thanks, Dr. Berriman.

Integra conducted a comprehensive search of the literature related to clinical studies in which SurgiMend was used in breast reconstruction. The literature review had rigorous inclusion criteria, and exclusion criteria were limited to those that would limit the quality of the data collected. The literature search found 27 scientific articles that addressed the safety and effectiveness of SurgiMend of note, and in support of Integra's confidence that the products used in the MROC study are the same as those cleared under K071807. All clinical references included a description of SurgiMend used in breast reconstruction that involved the configurations described in that 510(k).

In terms of effectiveness, patients reported high levels of satisfaction with breasts following reconstruction with SurgiMend. Specifically, BREAST-Q scores for satisfaction with breasts ranged from 85 to 88 following breast reconstruction in 251 patients for the total of 357 breasts reconstructed with SurgiMend. Of note, a score of 100 represents the highest level of satisfaction.

For safety, the totality of published evidence specifically related to SurgiMend supports that use of SurgiMend is no less safe than employing no ADM. Furthermore, no differences in complication rates were observed when comparing breast reconstruction with SurgiMend versus latissimus dorsi flap or other ADMs.

The clinical literature supports biocompatibility and mechanical support for SurgiMend. In an article by Scheflan et al., biopsies from 111 patients at the time of expander implant exchange showed persistence of SurgiMend, supporting long-term integration and continuous mechanical support during healing.

The image below shows the integration of SurgiMend 1 year following implantation with the region within the yellow border that is paler in color indicating the integrated SurgiMend device.

In a separate study by Gaster et al., capsule biopsies were obtained at the time of implant exchange from 12 patients with 17 breast reconstructions. The SurgiMend was clearly distinguishable both grossly and histologically out to 23 months.

The images show the tissue integration for one patient at 9 months after implantation of the expander and SurgiMend. The image on the left is an H&E stain with collagen in pink. The dense pink staining in the upper right portion of that image shows the SurgiMend device as confirmed by the center image which shows bovine Type I collagen staining green using immunohistochemical techniques. The image on the right shows staining for CD31 in red, indicating new vascularization at the margins of the SurgiMend device.

The study showed integration of SurgiMend by the patient's own tissue at the surface and within the fenestrations. It was observed that there was a minimal inflammatory response, the absence of a foreign body response, and no evidence of contracture. Collectively, the articles by Scheflan and Gaster show that SurgiMend is biologically and structurally stable through 2 years after implantation.

In summary, the clinical literature shows that women consistently report high levels of satisfaction with breasts after reconstructive procedures using SurgiMend.

The reported complications are those expected by surgeons with breast reconstruction procedures in general, with or without an ADM.

Finally, the data further support that SurgiMend meets the biocompatibility and mechanical design requirements for the intended use.

I will now pass it back to Dr. Berriman to describe our training plans and proposed post-approval study.

DR. BERRIMAN: Thanks, Dr. Gilbert.

SurgiMend has been widely used in breast reconstruction for over 10 years. For

surgeons seeking refresher training or additional experience in subpectoral SurgiMend implantation, as well as surgeons experienced with allograft ADMs but not SurgiMend, Integra will offer SurgiMend-specific training via a variety of learning platforms. For residents and attending surgeons, Integra intends to work in partnership with the American Society of Plastic Surgeons to support educational workshops that offer training for subpectoral breast reconstruction.

In our PMA submission, we have proposed a post-approval study. Integra intends to conduct a post-approval study that will supplement existing clinical evidence of SurgiMend's safety and effectiveness. We propose a prospective, 10 to 20 centers, observational study of 150 women. Each participant will be followed for 5 years to evaluate major complications and any adverse event related to device or procedure, as well as patient-reported outcomes. We look forward to working with the FDA to develop this study.

I will now request Dr. Gilbert to present the benefit-risk assessment for SurgiMend ABDM.

DR. GILBERT: Thank you, Dr. Berriman.

This Advisory Committee is asked to advise FDA on the specific questions of whether there is reasonable assurance that SurgiMend ABDM is safe and effective, and whether the benefits outweigh the risks for the proposed indication for use.

In my next slides I'm going to summarize the benefit and risk analysis. As we have discussed, SurgiMend has been used extensively for breast reconstruction throughout the U.S. since its introduction in 2007. There is a robust body of clinical literature that describes high levels of patient satisfaction with breasts when SurgiMend is used, and similar types and rates of complications observed compared with no ADM.

The pivotal SurgiMend study is based on the real-world data developed in the MROC

study that meets the CDRH criteria for relevant and reliable real-world data to support the premarket approval for the proposed indication. The SurgiMend study's statistical analysis plan, developed in collaboration with CDRH, and its results demonstrate that breast reconstruction with SurgiMend ABDM has a higher proportion of patients that met the criteria for composite clinical success compared to breast reconstruction with no ADM.

In summary, the totality of the evidence provides extensive support that SurgiMend ABDM is safe and effective, and the benefits outweigh the risks for its use in the treatment of women with immediate, two-stage, submuscular, alloplastic breast reconstruction in the United States.

As the Panel may be aware, when making benefit-risk determinations, FDA considers whether other treatments or diagnostics, including non-device therapies, have been approved or cleared for the intended condition and patient population. With that in mind, there is currently no FDA-approved biologically derived material indicated for use in post-mastectomy implant-based breast reconstruction, but an ADM is used in approximately 75% of the procedures in the United States. SurgiMend has been used in these procedures for over 14 years in the practice of surgery.

There is a reasonable assurance of safety. In the SurgiMend study, the pre-specified safety analyses strongly support that the complications were less frequent with SurgiMend than with no ADM. The incidence of complications for the SurgiMend group was 13.1 percentage points lower than for the no ADM control group.

When elective revisions and wound infections treated with oral antibiotics were excluded, the incidence of complications was still 4.9 percentage points lower than the no ADM control group.

The directional changes in the exploratory sensitivity analyses are consistent with the primary analysis for safety, which is based on the analysis of major complications that

comprise a component of the primary composite endpoint.

There is reasonable reassurance of effectiveness. The pivotal study demonstrates the benefits of SurgiMend in breast reconstruction compared to no ADM as measured by the effectiveness component of the composite primary endpoint.

In the propensity adjusted analysis, 44.5% of SurgiMend subjects and 39.1% of control subjects achieved success at 1 year compared with baseline regarding the Physical Well-Being (Chest) domain, indicative of the subject's perception of physical well-being at 1 year being restored to her perception of physical well-being prior to breast reconstruction.

Assessment of benefits and risks are well balanced. In the pre-specified novel endpoint that is highly clinically relevant to contemporary breast reconstruction surgery, the effectiveness and safety components are equally weighted. Specifically, a subject is counted as success only if she (1) meets the effectiveness criterion for success at 1 year compared with preoperative baseline regarding the BREAST-Q Physical Well-Being (Chest) domain, and (2) meets the safety criterion of absence of one or more postoperative major complications at 2 years or at 1 year if 2-year data are not available. This safety criterion in particular is very rigorous given the incidence of postoperative major complications associated with breast reconstruction surgery in general.

The primary endpoint analysis confirms the superiority hypothesis that a statistically significantly higher proportion of subjects in the SurgiMend group achieved composite clinical success compared with subjects in the control group.

The results of this analysis are supported by the directional changes that favor the SurgiMend group compared to the no ADM group in the multiple sensitivity analyses that were pre-specified in the statistical analysis plan.

Furthermore, the post hoc analysis proposed by FDA tested the primary endpoint superiority hypothesis. In the two institutions of the MROC study that used both

SurgiMend and no ADM, a higher proportion of subjects in the SurgiMend group achieved composite clinical success compared with the subjects in the control group.

Panel members, with this benefit-risk assessment in mind, you will be asked by FDA to provide feedback on the following questions that generally address the potential value of additional animal studies, bench studies, and a post-approval clinical study to provide further support for the safety and effectiveness of SurgiMend for soft tissue support in immediate, two-stage, submuscular, alloplastic breast reconstruction. I would like to share our thoughts on these questions for your consideration.

The first question is whether animal studies are necessary to address the time course of product absorption and tissue response to the SurgiMend device when used next to a tissue expander or breast implant.

There's not a widely accepted animal model for evaluating ADM in breast reconstruction surgery. The most common animal models involve quadrupeds, which make it difficult to simulate the mechanical environment of the breast. Furthermore, animal models tend to maintain well-vascularized tissue flaps that are less common in the clinical situation. The metabolic activity for most domestic animals pose additional challenges. We have received anecdotal reports that SurgiMend is absorbed in a porcine model at a rate that is much faster than observed in the articles by Scheflan and Gaster. Finally, long-term animal studies can be logistically challenging due to the relatively short lifespan of the animals and their unpredictable behavior.

In contrast, and as described in detail earlier, the studies by Scheflan and Gaster support the structural and biologic stability of the integrated SurgiMend device through 2 years in the presence of a tissue expander.

While those studies did not specifically address permanent implants, the SurgiMend study reports that 119 of the 179 breast implants had a smooth surface consistent with the

most common current practice of breast reconstruction surgery. The results show an abundance of long-term clinical evidence available from the published literature with 1,566 patients experiencing 2,174 breast reconstructions in which SurgiMend was used. It's hard to believe that there is limited value to be added by new large animal studies to evaluate SurgiMend in breast reconstruction procedures.

The second question is whether additional nonclinical bench studies are necessary to evaluate mechanical compatibility of SurgiMend PRS ABDM with the existing range of tissue expander and breast implant devices.

Bench studies are inherently limited in their predictive value as they diverge almost immediately upon initiation to the study, as the biologic response cannot occur. In a patient, the body immediately begins to integrate the SurgiMend into the adjacent native tissue. Further, a capsule forms between the tissue expander and the SurgiMend over the course of a few weeks, and the capsule is always present between the SurgiMend and a permanent breast implant after the exchange. So the bench studies failed to fully capture the environment in the patient.

That being said, the bench studies that are currently under way include a tissue expander with a textured surface and a smooth permanent breast implant in small and large sizes to account for different categories of implant surfaces at the extremes. While it is true that each type of tissue expander and breast implant may have differences in their surfaces, the myriad of products clinically available makes testing all combinations impracticable, not to mention the difficulty in obtaining the tissue expanders and breast implants from other companies, some of which are competitors. We believe the study design accounts for the general categories of concern and is further supported by the robust clinical experience in the SurgiMend study and reported in the published literature.

The final questions all deal with the proposed post-approval study. As stated earlier,

Integra intends to conduct a post-approval study that will supplement existing real-world evidence of SurgiMend's safety by following patients for 5 years to detect any long-term safety signals that may not have been detected during the 2-year follow-up period in the SurgiMend study. This 5-year time point is appropriate as clinical evidence supports that integration of SurgiMend has already stabilized by 2 years after implantation. We look forward to working with FDA to develop this study.

Panel members, FDA staff, ladies and gentlemen, based on the totality of available evidence, the premarket approval standard is met. There is reasonable assurance that SurgiMend PRS Acellular Bovine Dermal Matrix is safe and effective, and the probable benefits outweigh the probable risks when the device is used for soft tissue support in immediate, two-stage, submuscular, alloplastic breast reconstruction.

The current available evidence includes relevant and reliable real-world evidence and numerous published clinical studies.

Approval will enable the prior use of SurgiMend in the practice of breast reconstruction surgery to be addressed in device labeling and training programs and further evaluated in a post-approval study under FDA oversight.

Thank you for your time and attention. We would now be glad to answer questions from the Panel.

DR. LEWIS: I want to thank the Sponsor's representatives for their presentation, which was obviously quite well organized. We now have approximately 12 minutes for questions from the Panel.

I would like to begin with a question regarding the MROC study. In that study of approximately a thousand patients, SurgiMend was used in a minority, less than 200, 170 or 80, I believe, so the rest of the patients were the control group. Given the earlier information that virtually all patients today get some sort of supporting tissue, what was

used in those other 800 patients or so who were not in the SurgiMend study, what sort of -- if they did not have any sort of an ADM used, what was used in support because the evidence is that something is used in nearly all patients today.

DR. GILBERT: Yes, thank you for that question. The MROC study and the SurgiMend study should be delineated, I think, a little bit. The MROC study included ADM from a variety of other manufacturers. In the development of the SurgiMend study specifically, we only included subjects that were either no ADM or SurgiMend. So it's likely that, you know, some of the other competitor products were used in the MROC study but were not part of the inclusion criteria for the SurgiMend study.

DR. LEWIS: Okay, so there was not a comparison of SurgiMend versus other supporting devices, whether synthetic or not. You did indeed use only patients who had nothing used to support the gap between the pectoralis major and the serratus.

DR. GILBERT: That is correct. You know, as no ADMs are currently approved by FDA for use in breast reconstruction, it was most appropriate to evaluate the safety and effectiveness versus no ADM.

DR. LEWIS: Okay. My second question is, given that the ADM is made from bovine tissue, what accounts for the lack of any apparent antigenic reaction to that in patients in your pathological studies?

DR. GILBERT: That's a great question. The presence of the antigenic materials that have been studied extensively in the literature are primarily on the cell surfaces of the cells within the tissue. Due to the extensive decellularization process that occurs, those are largely removed along with all of the other cellular components. There's been extensive studies that have shown that decellularized materials from animals may have a very mild and transient response to the alpha-gal epitope, but generally speaking, that is transient and doesn't cause a sensitization effect.

DR. LEWIS: Thank you.

We'll now go to questions from the Panel and begin with Dr. Christianne Roumie.

DR. ROUMIE: Thank you. Christianne Roumie. I have a question for the Sponsor. Maybe all the surgeons were accepting of like the low amount of clinical success, but I found that really surprising, that there were really only between 20 and 30% of kind of the population had achieved clinical success.

My question actually relates to one of the sensitivity analyses. So in the statistical analysis plan there was a fairly high degree of missing data including about 25% and the assumption that that was used with no problems so that these people were imputed as success. My question is whether or not the alternate outcome, which is no clinical success, was considered in one of the sensitivity analyses and whether or not you could share that data because, in fact, I would argue that given the small number of people who actually had clinical success, that the alternate should have been the imputed outcome, which is no clinical success. Thank you.

DR. GILBERT: Thank you for the comments. Yeah, I think the first part of your question related to the overall level of composite clinical success. I think it in part reflects the rigorous criteria that was used with both a composite of the clinical safety of the product and the effectiveness component. And again, with the no ADM, which is the comparator group here, that was low and that was improved in the presence of the SurgiMend device.

To your question around the missing data and the imputation for no adverse events, we do actually have that analysis and I'll ask my colleague to share that on the screen. It's important to note that in the pre-specified analysis, the safety component of the analysis looks at, if the data was not available for complications at 2 years, the 1-year component was utilized instead. As you may note, the rate of missing data at 1 year was actually very

low, 0.8%, which represents a single subject with missing data for that time point.

And so you now see on the screen the original data had success in -- you know, this is not the composite clinical success, this is just for complications in 41 of the 119 patients with one of those patients imputed as no adverse event. If we were to look at the worst case, that one patient would have been deemed a failure, so it would've been 40 out of the 119 for a difference of less than 1% in the difference of the value.

We unfortunately are not able to provide how this estimate would carry forward to the composite clinical success. As noted in the presentation, Integra did not have access to the data, it was provided to FDA for the analysis, so we don't have this specific breakdown of patients to run that analysis.

DR. LEWIS: Dr. Hoffman.

DR. HOFFMAN: Philip Hoffman, University of Chicago. I have a question regarding whether -- of course, many of these patients will be candidates for chemotherapy following this initial part of the reconstruction implant and I was wondering whether there was any incidence of delays in getting chemotherapy started because of wound infections. And I recognize that the more minor infections treated with oral antibiotics were not considered major complications, but in my experience those aren't so rare and often do lead to delays in starting chemotherapy at the behest of the surgeon so that healing is not further retarded by starting chemotherapy. So were delays in getting chemotherapy started a problem?

DR. GILBERT: We're not aware of the data from the MROC study capturing that specific component. However, I would ask my colleague, Dr. Adelman, to come up and provide his perspective on that question.

Dr. Adelman.

DR. ADELMAN: Thank you. This is Dr. Adelman. Thank you for that question,

Dr. Hoffman. Your assertion is correct that in general, patients need to heal sufficiently well prior to starting adjuvant therapy, like systemic therapy. The MROC data, the SurgiMend study doesn't capture that specifically, but in my practice I have not seen, in general, that patients have a delay in starting their adjuvant therapies when I used SurgiMend.

DR. LEWIS: Dr. Ballman.

DR. BALLMAN: So I have several, but some of them are going to be really quick. I just want to confirm that for the missing data, and most of the missing data was not the major complications, so it was on the BREAST-Q that there was no worst-case scenario analyses done with respect to that, is that correct?

DR. GILBERT: That is correct, that we didn't have access to the data to run a worst-case scenario.

DR. BALLMAN: Okay. And then is there any long-term follow-up data with respect to the use of this device, like more than 2 years?

DR. GILBERT: The MROC study was limited to 2-year follow-up. There is some experience in published literature, although I'm not sure I could point to it immediately, we may be able to come back to that later, if desired. You know, the product has been utilized clinically for 14 years and again, we'd be happy to have Dr. Adelman share more of his experience, if that's desired.

DR. BALLMAN: No, that's fine, just a clarification question. And then there's no data also available with respect to the type of expander used with this and the type of breast implant?

DR. GILBERT: The manufacturer information was not provided to Integra. I assume it was not available in the MROC database. There is information about the surface and the fill rates, particularly for silicone fill and smooth surface that seemed to be the predominant implants used, but we don't have information about the manufacturer.

DR. BALLMAN: Okay. And then, thank you, one very last question. How confident are you that you will get, let's say, at least 90% 5-year follow-up in the post-study?

DR. GILBERT: We are confident that we will have the opportunity to develop methodologies to improve the data accountability for the study, through testing the case report forms and working closely with doctors that have pre-specified visits and working with FDA to develop methodologies. I should mention, we would be looking at electronic PROs to help facilitate those approaches and also limiting the number of the PROs that would be utilized to those that are most relevant to reduce the burden on the patient.

DR. BALLMAN: Thank you.

DR. LEWIS: Dr. Sandler.

DR. SANDLER: Thank you. Just a couple of quick questions. I think it was Dr. Adelman who mentioned that a randomized trial was attempted at MD Anderson and that one of the arms was dropped. I was just wondering, are there -- is there any data on the SurgiMend versus AlloDerm component of that trial that would be relevant?

And the second question also related to a statement of Dr. Adelman, that he uses this for prepectoral, products like this for prepectoral reconstructions, as well, and I was just wondering if there's going to be any claim or if there's any data on the risks and benefits in the prepectoral reconstruction procedure.

DR. GILBERT: Sure, thank you. Before I hand it off to Dr. Adelman to discuss the comments about the clinical study for the SurgiMend versus AlloDerm, the subject of this -- you know, the indication for use for this product, given the data that we're providing to the Panel for review, is in a submuscular/subpectoral approach. A prepectoral approach is out of scope of this indication and product usage. But I'll ask Dr. Adelman to speak to the clinical experience.

Dr. Adelman.

DR. ADELMAN: This is Dr. Adelman. Thank you for that question. The short answer is the studies that are currently available have looked at SurgiMend versus other ADM materials and there has been at least equivalency, if not potentially superiority in most of the published data when we look at SurgiMend compared to other ADMs.

In terms of subpectoral or submuscular versus prepectoral, the vast majority of two-stage implant-based reconstructions performed today are still subpectoral and as we learn more to use these materials and as there's a continuing evolution in the care we can provide to our breast cancer patients, I imagine that more surgeons will be looking at prepectoral as a way to use these materials.

DR. LEWIS: Dr. Leitch. You're muted.

DR. LEITCH: Yes, Marilyn Leitch. So my question is in the MROC study, what proportion of the patients had human ADM compared to the ones that had SurgiMend, and is there any data available that one could compare SurgiMend to?

My second question is regarding the follow-up issue and, like Dr. Ballman, I have concerns that if you can't get 2-year follow-up, and I think we've seen some of these problems in other devices related to reconstruction, of having patient outcomes is one of the big challenges in these studies and I think there needs to be very particular concepts about how that would be managed and what the failure problems were in the MROC study. And I'll stop with that.

DR. GILBERT: Thank you. This is Dr. Gilbert again. So to your first question, data that we received from the MROC analysis was limited to the SurgiMend product. However, I would draw your attention to the FDA safety notice from earlier this year that described that there were more complications associated with two other ADMs than the SurgiMend or AlloDerm or no ADM groups, but we don't have visibility to exactly how that analysis was conducted, how many subjects were included in that or be able to make any comparisons

between the SurgiMend and the AlloDerm in that instance. The --

DR. LEWIS: Dr. Campagni Portis.

DR. GILBERT: I'm sorry. The second part of the question, maybe if you wouldn't mind rephrasing.

DR. LEITCH: The issue of study design for long-term follow-up which has been notoriously difficult in devices around reconstruction.

DR. GILBERT: While we're confident in that we would develop methodologies to get good follow-up, we recognize the challenges that would occur and have been observed across a variety of different medical devices. I think that's a recognized inherent challenge, but again, we're working through the latest approaches to minimize that loss to follow-up. We look forward to working with the FDA to develop that trial and certainly would appreciate, per the question that you'll be asked, we appreciate any thoughts from the Panel as to how we can minimize that loss to follow-up.

DR. LEWIS: Dr. Campagni Portis.

DR. PORTIS: Yes, Natalie Campagni Portis. Well, I just do want to comment and reiterate what Dr. Ballman and Dr. Leitch said about follow-up. I know the Sponsor said that women want to know that ADMs are safe and that is really important, and without that long-term data we don't know that and we've met on this Panel before and seen the long-term effect of devices where we didn't collect the data. So I agree wholeheartedly with that statement and I'm sure we'll talk more about that.

I do have a question about what do we know currently about the impact of radiation on performance and adverse events.

DR. GILBERT: So your question is regarding what we know about the radiation in SurgiMend cases and the adverse events. I'd like to ask Dr. Adelman again to provide his clinical experience on that.

DR. ADELMAN: This is Dr. Adelman. That's a very important question and one that we at MD Anderson and certainly elsewhere around the world are trying to study. The hypothesis that I would have is that the use of an ADM, particularly SurgiMend, would have positive benefits for a patient in regards to radiation. I would hypothesize that the presence of an ADM may help decrease the incidence of capsular contracture which, around an implant, can be a challenge for a patient. Once the ADM is integrated, it may provide additional soft tissue support over the lifespan of the reconstruction such that radiation may be less deleterious. These are things that need additional study, for sure.

In our anecdotal experience, I have used ADMs for implant-based breast reconstruction in patients who have gone on to get adjuvant radiation therapy and although there's never 100% success in anything that we do, I do find that the use of ADMs improves our success rate in having good functional outcomes for those patients desiring definitive implant breast reconstruction after radiation.

DR. LEWIS: Dr. McCarthy.

DR. McCARTHY: Thank you. Colleen McCarthy here. I have two questions. My first one is I believe that as part of the composite clinical success, you looked at physical well-being at 1 year and major complications up to 2 years. My question is do we know what happens to physical well-being at the 2-year mark?

My second question is slightly related to outcomes, I'm wondering if you can give us a clinical snapshot as to how the complication profiles may or may not have looked different in the two groups.

DR. GILBERT: Thank you. The question is do we have information around the BREAST-Q at 2 years versus 1 year. I don't think I have that data at my fingertips. Would it be possible to review and come back later in the afternoon for that? Thank you.

DR. LEWIS: Yes.

DR. GILBERT: The second part with regard to the mix of complications, we don't have a precise breakdown on the complication mix between the two given the type of data that Integra was provided, so really our reliance upon the primary endpoints. However, we actually -- sorry, there is certainly in the exploratory analyses where we broke out the elective revisions and the infection with antibiotics, that was certainly -- we could show that and then on the -- I think we may be sharing with you a breakdown of the differences on the BREAST-Q component. So sorry, we're -- so this is showing the differences on the other elements of the BREAST-Q that were captured as secondary analyses. Again, all very similar in results.

DR. LEWIS: All right, could we go back to -- take the slide off, please.

Dr. Hickerson, you did not have a chance to introduce yourself at the beginning. Could you introduce yourself now and provide a brief discussion of your area of expertise, your institution and position there?

DR. HICKERSON: Yes, sir, I'll be happy to. Sorry for my tardiness. I'm Bill Hickerson, a plastic surgeon at the University of Tennessee here in Memphis, as a Professor of Surgery when I retired in December of 2020. My primary interest was not only within reconstruction for post-mastectomy where we've done a fair amount, nowhere near like that of other people that are on this Panel, but my primary work was within burns and reconstruction post-trauma where we have had the opportunity to use a lot of ADMs over the many years that we've practiced, which was some 35, 36 years.

DR. LEWIS: Thanks very much.

I would remind the panelists that in any future discussions today, if you wish to speak, if you'll indicate the raise hand function down at the bottom of your screen, that allows me to see you and recognize when you want to speak.

Not seeing any other questions at the moment, it's time for a break.

DR. MATARASSO: I have a question. I'm sorry.

DR. LEWIS: Oh, okay. Sorry, Dr. Matarasso.

DR. MATARASSO: I apologize. If you're out of time, I apologize.

DR. LEWIS: No, go ahead, we'll catch up on the time later.

DR. MATARASSO: Thank you very much. Thank you for that very comprehensive presentation. I would ask the clinicians that just presented if they -- presuming patient acceptance, if they envision a clinical situation in which they would not use this product on a two-stage reconstruction.

DR. GILBERT: So the question is, just to clarify, is there a clinical scenario in which the surgeons would not -- would be comfortable not using the SurgiMend if a patient --

DR. MATARASSO: Correct.

DR. GILBERT: -- the patient requested it not be used?

DR. MATARASSO: Presuming the patient was okay having it done, would this always be their preferred method of doing it? In other words, is there any scenario where they wouldn't want to use this or would they want to use it in the majority of the cases if it were available?

DR. GILBERT: Very good, thank you for that clarification. I'll ask Dr. Adelman to address that question.

DR. ADELMAN: This is Dr. Adelman. Thank you for that question, Dr. Matarasso. The short answer is, in any patient that I deem a good candidate for a two-stage implant-based reconstruction, using SurgiMend would be my preferred way to do it. There's no patient yet that would be a good candidate that I would be uncomfortable to use SurgiMend, assuming they didn't have a strong preference for some reason otherwise that was non-medically relevant. If the patient was a poor candidate for an implant-based reconstruction, perhaps due to smoking or other medical comorbidities, I would sooner

offer them a delayed reconstruction or consider non-alloplastic reconstruction as opposed to an implant reconstruction without using SurgiMend.

DR. MATARASSO: Thank you.

DR. LEWIS: Thank you. It's now time for a break, we're running a little behind.

DR. GILBERT: I'm sorry. I was going to ask Dr. Grant to also address the last question, if that's okay with the Panel.

DR. LEWIS: Okay, go ahead.

DR. GILBERT: Thank you.

DR. GRANT: Thank you, Dr. Matarasso. My answer is essentially very similar to Dr. Adelman. If I'm concerned about flap vascularity at the time of the immediate reconstruction, my algorithm would be to close and not use any device, whether it be an expander or an ADM, and then return for a delay basis, either device based or autologous, after we've had an assessment of healing of the mastectomy flaps. Thank you.

DR. MATARASSO: Thank you.

DR. LEWIS: All right, we'll now proceed to a break and instead of 15 minutes, we'll have the break for 10 minutes and we'll reconvene precisely at 10:55. Thank you.

(Off the record at 10:45 a.m.)

(On the record at 10:55 a.m.)

DR. LEWIS: I would now like to call this meeting back to order and we now will allocate 1 hour for the FDA to make their presentation of information relative to this application.

Dr. Ashar, will you be overseeing this?

DR. ASHAR: Yes, I think the team has it well in hand and if there's issues triaging the questions, I'll be participating with that portion.

DR. LEWIS: Thank you.

DR. ASHAR: Thank you.

DR. YOON: This is FDA's presentation regarding Integra LifeSciences Corporation's PMA for the SurgiMend PRS Acellular Bovine Dermal Matrix device, also known as SurgiMend PRS ABDM.

Hello, my name is S.W. Yoon, I'm a plastic surgery medical officer in the Division of Infection Control and Plastic Surgery Devices. I will be presenting the introduction and background.

Breast cancer is the second most common cancer in women after skin cancer. For patients who have undergone mastectomy to remove their breasts, either to treat or prevent breast cancer, breast reconstruction may be done to create the breast mound. It is estimated by the American Society of Plastic Surgeons that there were over a hundred thirty thousand breast reconstruction surgeries performed in 2019, and while there is a range of options for those who choose breast reconstruction, implant-based breast reconstruction is the most commonly performed form of breast reconstruction.

There are two types of breast reconstruction surgeries performed after a mastectomy, whether done at the same time as mastectomy or after mastectomy has healed. First option for breast reconstruction is the autologous tissue or flap reconstruction which uses tissue taken from another part of the body. However, today we are focusing on the implant-based breast reconstruction using either a saline-filled or a silicone gel-filled breast implant. For this particular PMA and indication, we will be focusing on the immediate two-stage submuscular approach to implant-based breast reconstruction as highlighted in blue.

Typically, for the first stage of an immediate, two-stage, submuscular, implant-based breast reconstruction, a temporary tissue expander is placed below the pectoralis muscle of the chest. Over the subsequent weeks or months, saline is injected into the port of the

temporary tissue expander until the desired expansion is achieved. In the second stage, the tissue expander is removed and replaced with a breast implant which is either filled with saline or silicone gel.

Since first described in literature in the mid-2000s, there has been an increase in the trend for physicians to utilize a mesh in implant-based reconstruction to support the tissue expander or breast implant in both subpectoral as well as prepectoral breast implant reconstruction. Over the past several years the use of mesh, particularly acellular dermal matrices or ADM, has increased and is now commonly used off label in the majority of all implant-based breast reconstruction.

Surgical mesh is typically a flexible thin flat sheet made of non-degradable synthetic materials, biodegradable synthetic materials, or from animal or human-derived tissues, ADM. Surgical mesh is a medical device regulated by the FDA and have been clear for other indications but not breast reconstruction.

This diagram illustrates how surgical mesh is typically used in two-stage, submuscular, implant-based reconstruction. It is placed in the first stage of the surgery along with the tissue expander. In the second stage of the surgery, while the tissue expander is removed and replaced with the breast implant, the surgical mesh is left in place.

While physicians can choose or choose not to use mesh in breast reconstruction, manufacturers have not come to the FDA and discussed the long-term safety and efficacy of the device on patients or discussed the risk-benefit profile.

To date, FDA has not cleared or approved any surgical mesh device, whether synthetic, animal tissue derived or human tissue derived, specifically indicated for breast reconstruction.

In March 2019, the FDA's General and Plastic Surgery Advisory Committee discussed

the evidentiary requirements needed to assess surgical mesh benefit versus risk in breast reconstruction. Trial design considerations identified by FDA at the March 2019 Advisory Committee meeting as critical for assessing surgical mesh of device safety and effectiveness for breast reconstruction included:

- Comparison to a control group that does not receive mesh;
- An assessment of at least one effectiveness endpoint;
- Inclusion and assessment of all relevant outcome variables;
- Analysis comparing treatment and control on both a per-breast and per-patient basis where feasible and appropriate;
- Pre-specified statistical analysis accounting for relevant confounding variables;
- Premarket follow-up of at least 1 year or until quiescence of inflammatory response and absorption: and
- Evidence of a favorable benefit-risk profile.

FDA believes that for patients who are choosing to have breast reconstruction after mastectomy to either treat or prevent breast cancer, the patients need to be able to make informed decisions. To ensure this, the FDA released a safety communication in March of 2021 informing patients, caregivers, and healthcare providers that certain ADM products used in implant-based breast reconstruction may have a higher chance for complications or problems. This was based on FDA's analysis of patient-level data from real-world use of ADMs for implant-based breast reconstruction which suggests differences in safety profiles among different brands of ADM, which was also supported by literature.

The safety communication was also to inform patients and healthcare providers that although ADM is used for other types of reconstruction, the FDA has not cleared or approved ADM for use in breast reconstruction.

I will now hand it over to Dr. Aguel to discuss how real-world evidence was used for the purpose of this PMA. Thank you.

DR. AGUEL: Thank you, Dr. Yoon.

My name is Felipe Aguel, I'm a deputy director in CDRH's Office of Clinical Evidence and Analysis. I will present some background regarding the clinical evidence that Integra included in their PMA.

The Mastectomy Reconstruction Outcomes Consortium, or MROC for short, study is a source of real-world data, and FDA and Integra recognized its potential after it was presented at the 2019 Advisory Panel meeting. It is a prospective observational cohort study of women of at least 18 years of age undergoing first-time breast reconstruction following mastectomy for breast cancer treatment or prophylaxis.

The MROC study enrolled 4,306 participants between January 2012 and February 2016. Participants were consented for at least 2 years of follow-up post-procedure. The consortium consisted of 11 high-volume sites in the U.S. and Canada, including nine academic centers and 58 surgeons.

The study captured procedures that use tissue expander and other autologous tissue reconstruction techniques. The study captured routinely collected patient care data, as well as patient-reported outcomes. The patient-reported outcomes collected include validated scales from the reconstruction module of the BREAST-Q questionnaire, some of which were qualified in 2019 by FDA as validated Medical Device Development Tools or MDDTs.

FDA supports the use of relevant and reliable real-world data that are fit for purpose for regulatory decisions.

The MROC study captured data on procedures with and without ADMs. Four brands of ADMs were predominantly used in those procedures that use an ADM, including SurgiMend.

Integra's PMA relies on real-world evidence, or RWE, resulting from a prospective analysis of existing observational study data to support a change in the indications for use of the SurgiMend PRS ABDM. Specifically, it relies on a comparison of cohorts of MROC study participants whose procedures included use of the SurgiMend ABDM to a cohort of participants whose procedure did not utilize an ADM.

FDA worked with the owner of the MROC data to find a solution for Integra to use the data without unauthorized disclosure of information. This solution required that FDA receive the data and conduct an analysis designed by the Sponsor without disclosing subject-level information to Integra.

After receiving the MROC subject-level data, FDA conducted an initial assessment for relevance and reliability and an assessment whether the data could meet the seven factors identified at the 2019 Advisory Panel meeting. Integra then prospectively defined a statistical analysis plan in close collaboration with FDA. Recall that FDA obtained access to de-identified subject-level MROC study data and that Integra did not and still does not have access to that subject level MROC study data. It is crucial to note that FDA took care to remain blinded to and the Sponsor did not have access to study outcomes as they worked to define the statistical analysis plan.

FDA then conducted the analysis according to the prospectively defined analysis plan and summarized the results of the analysis. FDA provided summary results of the analysis to Integra subject to limitations in order to maintain patient confidentiality. Integra included the summary results of the analysis in their PMA to support the safety and effectiveness of the SurgiMend PRS ABDM for the proposed indication.

Like all potential sources of valid scientific evidence, real-world evidence has its strengths and limitations. Strengths include that RWE can be indicative of performance under real-world use conditions and that it can leverage existing data. Limitations include

the potential for missing data and the potential for measured and unmeasured confounders.

However, it is important to keep in mind that no source of valid scientific evidence is limitation free. Many of the limitations listed on the slide are also true of prospectively enrolled clinical trials conducted under a strict follow-up schedule. It is also important to keep in mind that limitations with real-world evidence like those of clinical trials can be mitigated with careful a priori planning and prospective definition of study methodology.

This is the reason why Integra, in close collaboration with FDA, prospectively defined a statistical analysis plan that included:

- Pre-specified inclusion/exclusion criteria to ensure the analysis population is consistent with the intended use population;
- Pre-specified propensity score methodology to balance known covariates across study arms;
- Pre-specified imputation methodology to address missing data; and
- Pre-specified sensitivity analyses to assess robustness of findings.

Thank you for your attention. With that, I would like to turn it over to Dr. Treviño and the FDA review team.

DR. TREVIÑO: Thank you, Dr. Aguel.

My name is Elda Treviño and I'm the lead reviewer for this file in the Office of Surgical and Infection Control Devices. Today I will discuss the SurgiMend device as well as nonclinical components of the PMA submission.

The following list is the PMA review team. Please note the bolded names at the top indicate reviewers that will present today on behalf of FDA.

The FDA would also like to acknowledge members of the team that worked on conducting the analysis of the MROC dataset listed here.

The subject device is composed of intact extracellular collagen fiber matrix derived from fetal bovine dermis. The dermis is decellularized through a series of chemical and physical processes and then subsequently freeze dried and fenestrated. The device requires a saline soak prior to use and has a shelf life of 5 years.

The image on the top right is a representative image of the subject device. The table immediately below lists the available sizes and shapes of the subject device.

There were two FDA-cleared SurgiMend devices available during the MROC study; one ADM derived from fetal bovine tissue and one ADM derived from neonatal bovine tissue. Both cleared devices have indications for implantation to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue membranes.

The Sponsor proposed several nonclinical studies in their submission including biocompatibility testing. While biocompatibility testing has been conducted on the previously cleared SurgiMend devices, including cytotoxicity, sensitization, intracutaneous reactivity, acute system toxicity, genotoxicity, intramuscular toxicity, hemolysis and pyrogenicity, the standards for biocompatibility testing have evolved since SurgiMend was first cleared in 2007. Thus, the Sponsor has opted to execute confirmatory biocompatibility tests. The tables on the right are the biocompatibility testing for the final finished sterilized device which includes both animal and bench testing. This testing is expected to be completed by February 2022. This afternoon, the Advisory Committee will be asked to comment on whether additional animal studies are needed.

An important consideration for the SurgiMend device is that it will always be in contact with another device, mainly a tissue expander or breast implant. This contact can cause the devices to interact with one another. Thus, the Sponsor has proposed mechanical testing of a tissue expander and breast implant device alone and in combination with the subject device.

Following mechanical testing of the individual and coupled devices, the Sponsor will conduct chemical analyses on the soluble and insoluble fractions of the wear fluid used during mechanical testing. Additionally, the surface properties and tensile strength of all the devices will be assessed.

The Sponsor has proposed to perform the mechanical compatibility testing with one type of tissue expander and one type of breast implant. Mainly, as shown on the right, they will test both a small and large textured tissue expander and a smooth silicone-filled breast implant, both from the Mentor brand. The testing is expected to be completed by March 2022. The Advisory Committee will be asked to comment on whether additional mechanical testing is needed.

I will now hand it over to Dr. Yoon to discuss the SurgiMend study.

DR. YOON: The SurgiMend study is a prospective comparison of existing data to evaluate SurgiMend (treatment) versus no ADM (control) in immediate, two-stage, subpectoral, implant-based reconstruction from subjects enrolled in MROC study, which was described by Dr. Aguel earlier. The device is SurgiMend; however, the exact iteration of the SurgiMend device used is not clear. There were 11 sites in the U.S. and Canada, as discussed by Dr. Aguel earlier; however, with the de-identified nature of the data, surgeon performance variability, site to site or regional variability are unknown. Those who were included in the SurgiMend study were limited to females, first-time breast reconstruction with immediate, two-stage, implant-based, submuscular breast reconstruction after mastectomy in either unilateral or bilateral reconstruction including women for cancer prophylaxis. Excluded from the study were those who had elective reconstruction following complications of breast augmentation, mastopexy or breast reduction, procedures performed following previously failed attempts at breast reconstruction, flap surgery, and combination of different ADMs or bilateral reconstruction with unilateral SurgiMend use.

For demographics, there were a total of 119 patients in SurgiMend cohort and 868 patients in the no ADM control cohort. The total breasts treated were 179 in the SurgiMend cohort and 1401 in the control. Mean age differed by approximately 2 years in the two groups. Mean BMI were similar between the two groups at 25.7 and 25.8 in SurgiMend and control. For smoking status, the percentage of those who never smoked were higher in SurgiMend group at 72% compared to 62% in the control group. For race, 83% of SurgiMend group and 85% of the control group are categorized as white. And 86% of the SurgiMend group and 93% in control were being treated for breast cancer.

More patients in the control group had bilateral reconstruction at 61% compared to 50% in the SurgiMend group. For chemotherapy, more patients in the control group, 35% versus 20% in the SurgiMend group, had received adjuvant chemotherapy with more in SurgiMend group, 23% receiving neo-adjuvant chemotherapy compared to 15% in control group.

Demographics per breast show that 62% in SurgiMend group and 64% in control group were for breast cancer treatment. For mastectomy, simple and modified radical mastectomy made up for 88% of the SurgiMend group and 87% of the control group. For radiation, 22% in SurgiMend group and 26% in control group received radiation therapy.

For tissue expander and breast implant characteristics, information on tissue expander characteristics were, for the most part, unavailable. For breast implant, manufacturer information was also mostly not available.

In both SurgiMend and control group, silicone gel-filled breast implants were used more, 76% in SurgiMend group compared to 63% in the control group. For surface texture of the silicone breast implant, while both groups had more smooth surface implant reported as 67% in SurgiMend and approximately 50% in control group, there were more textured breast implants reported in the control group at 22% compared to the 9% in

SurgiMend group. Of note, information on surface texturing was missing and approximately 24 to 29% of implants in both groups. For breast implant size, the mean was 462.6 for SurgiMend compared to 496.4 for control group.

Clinical success criteria of the study was pre-specified as the proportion of subjects who achieved a composite clinical success of two endpoints. The first component was change of BREAST-Q Physical Well-Being (Chest) score from baseline is no less than -4 points at 1 year post-implant and second, absence of major complications through Year 2 or through Year 1 if Year 2 data were not available. The major complications were defined for the study as hematoma, explantation, reoperation, capsular contracture, infection, dehiscence, tissue necrosis, implant rupture, and seroma.

Based on the pre-specified clinical composite success criteria, more proportion of patients in SurgiMend group achieved success criteria compared to the control group. The estimated primary clinical composite success rate was 32.4% for the SurgiMend and 21.1% for the control group. The clinical composite success rate for SurgiMend group was statistically significantly higher than that for the control group with a two-sided p-value of 0.02. Of note, 37% of SurgiMend subjects and 47% of control subjects had data missing for 1-year change of BREAST-Q Physical Well-Being (Chest) score. For major complications at Year 2 or Year 1 if Year 2 data are not available, one SurgiMend subject and 20 control subjects were missing major complication data. Details of the statistical analysis and missing rates will be presented later by Dr. Zhao.

The major complications as pre-specified were already included in the clinical composite success criteria. For comparison of those major complications in SurgiMend versus control at Year 1 and Year 2 post-op, this was provided in the Executive Summary in Table 15. For other serious adverse events such as death incidents and narratives, due to the de-identified nature of the study, this information is not available.

In addition, although reoperations, as pre-specified, included all reoperations including for elective revisions, the reasons for elective revisions were not available.

In addition, MROC collected clinical data including complications defined as adverse surgery related postoperative events requiring additional treatment, and therefore it is unclear whether adverse events such as systemic, rheumatological or neurological symptoms or red breast syndrome were collected nor were they available.

This study was designed with a 2-year follow-up, therefore there's no assessment of the potential impact of ADM use on breast implant performance or the potential impact on cancer recurrence or breast implant-associated anaplastic large cell lymphoma. There were other secondary endpoints that you reviewed in the Executive Summary; however, the study was not powered nor designed to assess for differences in those outcomes.

The Sponsor provided a post-approval study to address some of the clinical questions not addressed by the MROC study. The Advisory Committee will be asked whether a post-approval study is needed for the SurgiMend PRS ABDM, if approved. If a post-approval study is needed, the Advisory Committee will be asked if the proposed post-approval study is acceptable. If not, the Advisory Committee will be asked to recommend changes to the proposed post-approval study.

Additionally, the Advisory Committee will be asked whether there is reasonable assurance of safety and effectiveness for the proposed indication, and whether benefits outweigh the risks.

I will now hand it over to Ms. Debbie Fellhauer to discuss medical device reports. Thank you.

MS. FELLHAUER: Good morning, my name is Deborah Fellhauer and I am the Assistant Director in the Division of Infection Control and Plastic Surgery Devices. I will be speaking to you today about the medical device report analysis of the SurgiMend device.

FDA considers a total product life-cycle paradigm. As such, data is collected and evaluated at all stages of the device life cycle, including both premarket and postmarket stages.

The system for universal surveillance houses medical device reports, or MDRs, submitted to the FDA by mandatory reporters: manufacturers, importers, and device user facilities; and voluntary reporters such as healthcare professionals, patients, and consumers. The FDA uses MDRs to monitor postmarket device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of devices. While the MDR system is a valuable source of information, this passive surveillance system has limitations including incomplete, inaccurate, untimely, unverified, or biased data in the reports. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential underreporting of events and lack of information about frequency of device use.

An MDR search was performed for SurgiMend adverse events. The search produced 123 MDRs which were individually reviewed. Of the 123 MDRs, 48 reports specifically mentioned use in breast surgeries, which is where the analysis was focused.

There were 18 reports of immediate reconstruction with tissue expanders resulting in flu-like symptoms and poor wound healing. The reports also included mention of pain, edema, redness, and dehiscence; 10 reports of infections including *Pseudomonas*, *Klebsiella*, *Staph aureus*, and gram negative. Of these 10 reports of infection, 50% do not mention if a culture was performed and 50% report that a culture was obtained; however, not all report the results.

Seven report either hypersensitivity, erythema or irritation or a combination of the three. Five are publications, four report seromas, one MDR reports multiple cases of capsular contracture and the physician has opted to stop using SurgiMend; one report of

red breast, one report of a split breast with pus, no cultures obtained; and one report of the SurgiMend tearing during implantation.

This bar graph illustrates the timeline for when the 48 MDRs were received for the SurgiMend devices that were specifically used in breast surgeries with no obvious trend noted.

This table lists the top ten patient and device problem codes reported in the 48 breast surgery MDRs. The patient problems include edema, fever, erythema, pain, impaired wound healing, dehiscence, unspecified infection, hypersensitivity/allergic reaction, malaise, and ill-defined complaint.

I will now turn the presentation over to Dr. Zhao.

DR. ZHAO: Thank you, Ms. Fellhauer.

My name is Yu Zhao and I am the statistical reviewer in the Office of Clinical Evidence and Analysis at FDA. I will present statistical analysis plan and result of the SurgiMend study.

The SurgiMend study to support this PMA was analysis of a subset extracted from the existing MROC study data using a prospectively developed analysis plan to compare SurgiMend versus no ADM in immediate, two-stage, submuscular, implant-based breast reconstruction. Here, the MROC study was a prospective, multicenter, observational study of subjects who underwent a post-mastectomy reconstruction treated with various reconstruction techniques.

As presented by Dr. Aguel, since the MROC patient-level data are available to FDA but not the Sponsor, the statistical analysis plan was developed through a collaboration between the Sponsor and FDA. The analyses were then conducted by FDA per the SAP; and the result summary was provided to the Sponsor.

Among 4,306 MROC study subjects enrolled from January 2012 to February 2016 per

the pre-specified inclusion/exclusion criteria listed on the right, 1792 subjects were identified to have undergone immediate, two-stage, submuscular, IBBR. Nine hundred eighty-seven of the subjects were treated with either SurgiMend or control (no ADM) and were included into the SurgiMend study. The treatment SurgiMend group only included subjects with the use of SurgiMend and 119 MROC subjects from two sites were included. The control (no ADM) group only included subjects without use of mesh and 868 MROC subjects from nine sites were included.

The pre-specified primary endpoint was the composite clinical success referred to as CCS. A subject is deemed a composite clinical success if both of the following two criteria are satisfied. Criterion 1: change of BREAST-Q Physical Well-Being (Chest) score from baseline is no less than negative 4 points at 1-year post-implant. And Criterion 2: absence of major complications through Year 2 or through Year 1 if Year 2 data are not available. Here, the major complications include hematoma, explantation, reoperation, capsular contracture, infection, dehiscence, tissue necrosis, implant rupture, and seroma. The CCS rate is the proportion of subjects with composite clinical success.

A superiority hypothesis test for the primary endpoint was pre-specified to compare the SurgiMend group to the control group regarding the CCS rate. The test was planned to be conducted at a 2-sided alpha level of 0.05 using a Z test. The pre-specified primary analysis population was the full analysis set, referred to as FAS, which included all 987 subjects who enrolled into the study, provided informed consent, and received the study intervention. In the primary analysis, missing CCS data were to be imputed through multiple imputation. No formal hypothesis tests were pre-specified for the safety endpoints and the secondary endpoints.

As the SurgiMend study was an analysis of a subset extracted from the existing MROC study data, potential confounding due to unbalanced distributions of baseline

covariates between the two study groups was of concern. To mitigate potential confounding, a propensity score-based stratification approach was used to design the SurgiMend study. The propensity score stratification study design was finalized without any access of MROC clinical outcome data. As a key assumption required for this design, it is assumed that there are no unmeasured confounders. In other words, we assumed that all potential confounders are controlled in the propensity score model.

At first, a logistic regression model was fitted to derive the estimated propensity score which was a probability that a subject received the treatment of SurgiMend instead of the control given the subjects observed baseline confounders. The 21 terms in this table on the slide were included in the propensity score model. Please note that patient-level surgeon data were not available for this analysis and the factors related to site or surgeon were not included in the propensity score model.

With the propensity score stratification approach, study subjects are stratified into multiple strata based on the estimated propensity scores. Within each stratum, the study can be conceptualized as a quasi-RCT and observed covariates are better balanced between the study groups under the assumption that there are no unobserved confounders and the propensity score model has been correctly specified. For treatment effect estimation, at first, within each stratum, the treatment effect can be estimated through direct comparison between the two study groups; then the stratum-specific estimates of the treatment effect can be pooled across the stratum to estimate the overall treatment effect.

In the SurgiMend study, the study subjects were stratified into five strata according to the propensity score quintiles of the SurgiMend subjects so that each stratum had a roughly equal number of SurgiMend subjects. The numbers of subjects by study group in the five strata are presented in the table.

The box plot of the propensity score distribution per stratum for each study group

was constructed and presented in the figure on the left. It shows acceptable overlap in propensity score distribution between the two study groups in each stratum.

To further assess baseline covariate balance between the two study groups with the propensity score stratification, the average standardized differences over the five strata for baseline covariates were calculated. With the propensity score stratification, the average standardized differences over the five strata are less than 0.1 for all controlled baseline characteristics, indicating acceptable covariate balance between the two study groups. The presented study design with propensity score stratification was agreed by all stakeholders. Subsequently, clinical outcome data were unblinded and analyzed.

The pre-specified primary estimand was average treatment effect on the treated, referred to as ATT. ATT is the population average of treatment effect of those subjects who ultimately received the treatment. In addition to ATT, another estimand, average treatment effect (ATE), was planned to be assessed as a sensitivity analysis. ATE is the population average of treatment effect of moving an entire population from control to the treatment.

The data accountability of the primary endpoint, CCS, is summarized in the table. The missing rate for the primary CCS was 25%. Thirty-seven percent of SurgiMend subjects and 47% of the control subjects were with missing data regarding 1-year change from baseline in BREAST-Q Physical Well-Being (Chest) score. In addition, one SurgiMend subject and 20 control subjects were with missing major complication data.

The observed results of the primary endpoint, CCS, for each stratum for the two study groups are summarized in the table. Based on the completers, the observed CCS rate was higher in the SurgiMend group compared to the control in each of the five strata.

For the primary analysis of CCS, missing BREAST-Q Physical Well-Being (Chest) score data were imputed through multiple imputation, and the 21 subjects with missing major

complication data were imputed as no events. The CCS rate per each stratum for the two study groups with multiple imputation are summarized in this table. With multiple imputation, the estimated CCS rate was higher in the SurgiMend group compared to the control in each of the five strata.

With the pre-specified primary ATT approach together with multiple imputation, the estimated CCS rate was 32.4% for the SurgiMend group and 21.1% for the control group. The estimated difference in CCS rate between the SurgiMend and the control groups was 11.2% with a 95% confidence interval of 1.7% to 20.8%. The primary endpoint CCS rate was statistically significantly higher in SurgiMend compared to the control with a two-sided p-value of 0.02.

As a sensitivity analysis, the hypothesis test regarding the CCS was conducted based on the ATE approach with multiple imputation. As shown in the table, the estimated CCS rate was 32.4% for the SurgiMend group and 22.3% for the control group. The estimated difference for CCS rate between SurgiMend and the control was 10.2% with a 95% confidence interval of -1.1% to 21.4%, covering zero. No statistically significant difference in the primary CCS rate was detected between the two study groups with a two-sided p-value of 0.08. The plot on the lower right corner is a visual presentation of the reported results.

In summary, the SurgiMend study was an analysis of a subset extracted from the existing MROC study data using a prospectively developed analysis plan.

The study design with a propensity score stratification approach was implemented to mitigate potential confounding bias.

With a pre-specified primary ATT analysis and implementation of multiple imputation, primary endpoint CCS rate was statistically significantly higher in SurgiMend compared to the control.

At the same time, the SurgiMend study also has the following limitations. First, even with a propensity score stratification study design, potential biases may still remain due to unobserved confounders. Second, approximately 25% of CCS data are missing.

That concludes the FDA presentation. We thank the Panel for their time and attention and look forward to your deliberations. FDA is happy to address your questions.

DR. LEWIS: All right, I thank the presenters. We'll now have questions from the panelists for the FDA. Let's begin with Dr. Ballman.

DR. BALLMAN: Hi, yes. This is Karla Ballman. Thank you very much for the presentation. I have several sort of short questions. One is was there any comparison of how the two sites that actually used the SurgiMend, how did those two sites compare to the majority of sites that did not?

And in addition, did you look at patient characteristics, demographics and so forth at baseline between those that received SurgiMend and those that received other ADM products?

DR. ASHAR: This is Binita Ashar. The team has presented the information that they have regarding their analyses. Some of your questions are ones where I can confer with them and perhaps get back to you after the next break with a little bit more details on what they have. But for the most part, the analysis they provided is complete --

DR. BALLMAN: Okay.

DR. ASHAR: -- in any case, if there was missing information.

DR. BALLMAN: Okay, great. And then another question is how confident is the FDA that in a post-marketing study there will be 5-year follow-up data on let's say more than 90% of the patients given that even in MROC, which seemed to be a very well designed study, they were missing lots of data even at 1 year.

DR. ASHAR: You know, FDA -- this is always a challenge in the postmarket space and

we would appreciate any recommendations that the Panel may have pertaining to milestones or other measures that the Agency may take to assure that there is good follow-up.

DR. BALLMAN: Okay, then one last question. I just want to make sure that we're not being asked to say whether there's evidence that this is an efficacious device.

DR. ASHAR: There's going to be questions at the end of your deliberations and those questions involve assessment and benefit versus risk, as well safe and effective per our regulations.

DR. LEWIS: I think the answer to your question, Dr. Ballman is yes, you will be asked to reach a conclusion.

Dr. Compagni Portis.

DR. PORTIS: Thank you. Natalie Compagni Portis. Do we have any data on the incidence of breast cancer recurrence or the incidence of secondary cancers or autoimmune disorders and how the ADM may play into the complications we've seen with implants?

DR. ASHAR: This is Binita Ashar from FDA. So the information that the team has presented is the 2-year follow-up data that they received. We don't have any follow-up beyond that time point other than the information that's already provided in the literature. And if that is something that the Panel wishes for the Agency to explore further, any recommendations around that would be helpful.

DR. PORTIS: Thank you.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: It was mentioned by Dr. Yoon, I believe, that the implant type was textured implant, 22%, and the no ADM and 9% in the SurgiMend. Do you think that that would impact the data outcome, that difference between the two, and could have influenced choices for use of the ADM?

DR. ASHAR: I think your question is a legitimate one. It may be possibly addressed by the company, and I'm also being informed that we may have some information related to breast cancer recurrence and that would require a little bit of analysis by our team to come back to you after the lunch break with that information.

DR. LEWIS: Dr. Sandler.

DR. SANDLER: Thank you, Howard Sandler, Cedars-Sinai. One of the variables that was indicated in the MROC study was radiation, yes or no. The Sponsor mentioned, sort of anecdotally, that they didn't seem to see increased complications with ADM in patients receiving radiation. I was wondering whether the MROC study looked at that specifically and whether there's any estimate of whether use of radiation in ADM increased or decreased toxicities or response in terms of the study outcome.

DR. ASHAR: Thank you for that question, Dr. Sandler. I'm going to turn to my FDA colleagues, either Dr. Felipe Aguel or his colleague, Veronica Sansing-Foster, to be able to comment on whether we received data pertaining to radiation effects.

Dr. Aguel, are you able to address?

DR. AGUEL: Thank you, Dr. Ashar. Let me turn my video on, good. We do have the information in the dataset but that analysis was not conducted. The subgroup analysis by radiation was not conducted.

DR. SANDLER: Radiation and breast reconstruction, it's sort of a known -- there's a known adverse impact of radiation on the outcome. Was there a reason why you didn't look at that association?

DR. ASHAR: This is Binita. I think, you know, you're asking a great question. This is together with the concept of recurrence. We will look into the matter regarding radiation effects and see what more we can provide.

DR. AGUEL: And Dr. Ashar, if I may, I'm being informed here that that was included

in the propensity score analysis in the propensity score model, but we don't have a subgroup analysis, it's something that we can look into and get back to the Panel.

DR. SANDLER: Just if I might, just a quick follow up. Does FDA think it would be reasonable or feasible to add a radiation analysis to the subsequent study that the Sponsor might do if asked to complete a follow-up study or would it be a waste of time to add a radiation variable?

DR. ASHAR: I think that's exactly why we're here. We're looking for your vast recommendations on what additional data, if any. If the Panel comes to a favorable decision and you wish to have a post-approval study, any and all recommendations around what can provide informative information for patients and providers and how to assure compliance with that study would be sincerely appreciated.

DR. SANDLER: Thank you.

DR. LEWIS: Dr. Li. You're muted, Dr. Li. Unmute yourself.

DR. LI: How's that?

DR. LEWIS: Better.

DR. LI: Thank you. I have a question on preclinical mechanical testing. What evidence is there, in your study, of mechanical damage to the implant either caused by the breast or otherwise? And the reason I'm asking that question is if you need to identify how the device was damaged before you can develop a reasonable laboratory test. So if you just take a mesh, an implant, and put them together and rubbed them together or load them somehow, you need to have some confidence that what you get from the laboratory test matches what you see clinically.

So my question is two parts. From your study, either study, have you looked at retrieved implants and if they mechanically failed, how did they mechanically fail? And if you identified those mechanical failures, how did you develop the laboratory tests, the tests

for that?

DR. ASHAR: This is Binita Ashar from FDA. So FDA did not perform the mechanical testing associated with this device, but this is a great question probably best addressed by the company.

I'm not sure, Mr. Chairman, if the company should weigh in at this point or if you'd like for them to comment at a later time.

DR. LEWIS: If the company is available to comment, it would be appropriate to do it now. If they're available, we would welcome their comments.

DR. GILBERT: The company is available now.

DR. LEWIS: Fine, go ahead. Thank you.

DR. GILBERT: So we've not observed clinical failure of the SurgiMend device, as reported. I will note the FDA mentioned that there had been some MDRs that showed tearing at the time of implantation, but that is different. So as we developed the compatibility testing, the silicone implants and tissue expanders, we really relied on the standards that had been developed to evaluate these materials and working with a CRO that has extensive experience in this working with silicone breast implant manufacturers to evaluate that.

That being said, we totally acknowledge the comments from Dr. Li, there are limitations in the bench testing and, as I mentioned in the presentation, there are -- it omits the biologic response that we would see that would be an important consideration that hasn't been taken into account, clearly, in the clinical evaluation of these materials.

DR. LEWIS: Dr. Li, do you have any further questions?

DR. LI: No, just a comment. I'm a little uneasy in this regard because there were a lot of unknowns about exactly what implants were used, if they were textured and who the manufacturer was, and it's not clear if there's just a mesh failure or an implant failure or if

there is some combination caused by the interaction of the two. So we seem to be having a lot of unknowns and we're developing or you're conducting mechanical testing in the laboratory for which we have no connection to the actual clinical experience, so I'm not sure how we close that gap.

DR. LEWIS: Dr. Coleman, did you want to respond?

DR. GILBERT: This is Dr. Gilbert, sorry.

DR. LEWIS: Oh, sorry.

DR. GILBERT: I should have announced myself earlier.

DR. LEWIS: Sorry.

DR. GILBERT: Again, given the nature of the complications that were observed, most of these were reoperations, elective revisions being the most common, we didn't see extensive or frequent implant rupture, and so in the safety profile per the SurgiMend study and confirmed in the clinical literature, it's quite strong. So there aren't a lot of safety indicators that would lead us to specific questions for the design. I think we're probably looking more at the bench testing.

Clearly, with the mechanical -- you know, mechanical components and surface texture is really a worst-case scenario given that it wouldn't have the benefit of the capsule between the materials or the tissue integration that would be there and a lot of this would be really the focus on the biocompatibility aspects, as well. So I think clearly, there's limitations in the bench studies but we do think that there's going to be valuable information to supplement the totality of clinical evidence.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: Thank you for calling on me. I've been struck in both the -- throughout the entire presentation to us, as a Panel, by both the manufacturers and the FDA, that we've been talking a lot about real-life chemical and mechanical testing, but there

really hasn't been any discussion at all of cytologic studies of the material and I think questions remain or they may be in case reports, but I don't know of an organized study that has really been dealing with what happens to the inner surface of the ADM as it becomes part of the capsule around the breast implant. I think we need to understand cytologically what the cells are doing, whether it be a capsule that forms on the inner surface of the ADM is the same as the capsule around the rest of the breast implant. I think there's a lot of reasons for that and I think we also need to know the answer to that over time because as the manufacturers mentioned, this is a biodegradable device, it's something that's incorporated, it's -- I'm sorry, it's replaced, it's not incorporated.

So my question would be if we knew what the lifespan of the material was more with -- you know, more accurately on ranges of short and long, I think it could help us decide how long the follow-up should be for any kind of postmarket surveillance because if there are cytologic changes and somehow they alter as the device is completely resorbed over some period of time, then I would imagine that unless there were permanent changes, the follow-up wouldn't have to be many, many years longer. But I think that we need that information to kind of make those finer distinctions about how long this has to be looked at. Thank you.

DR. ASHAR: This is -- oh, go ahead, Dr. Lewis.

DR. LEWIS: No, I was just going to ask you to comment, Dr. Ashar. There's not a direct question, but you may want to comment.

DR. ASHAR: Certainly. I think this is information that perhaps Integra may have to be able to help inform the Panel's deliberations on this topic, so my recommendation would be to see if Integra has any additional information and then just the others on the Panel, with their expertise.

DR. LEWIS: Dr. Gilbert, are you prepared to address that now or address it later?

DR. GILBERT: This is Dr. Gilbert, I'm happy to address that now.

DR. LEWIS: Great, go ahead.

DR. GILBERT: Yeah, as we described, in the company's presentation, again, the importance of the histologic and the tissue integration response, which was the focus of two clinical studies by Dr. Scheflan with 111 patients and most particularly in the study by Dr. Gaster et al. And it really does address, to a large extent, the questions that were raised by Dr. McGrath in that we see that over a period of 2 years that the product is not resorbed, it is actually integrated into the surface, into the surrounding tissue at the margins, primarily, with new connective tissue being deposited and vascularization.

But the studies suggest that there is really a stability that is developed, a homeostasis that occurs within the first year and that that doesn't change over the course of the second year, and it is distinct from the capsule that forms adjacent to the implant so it provides that separation between the silicone implant and the integrated tissue. And so that's part of the consideration to the 5-year proposal is that there's not an inflammatory response, there's not a foreign body response that is observed within those first 2 years and that we expect that it's really stabilized such that the 5-year time point is appropriate as things are stabilized within that setting.

DR. LEWIS: Dr. Gilbert, let me just add an add-on question to what's being discussed. How quickly in your studies, if you have data, does a tissue barrier develop between the silicone breast implant and the dermal matrix?

DR. GILBERT: That capsule form, it's going to obviously vary depending on the patient, but it's happening in the course of weeks after the implant surgery.

DR. LEWIS: Okay. Dr. McGrath, do you have any follow-up to that?

DR. McGRATH: My only other question would be in what way does that capsule differ from the capsule that is formed on the surface of the silicone implant?

DR. GILBERT: I don't have -- I'm not prepared to answer that question at this point. I want to refer back to the articles that I just discussed which describe the morphology and histologically. I could come back with more on that later if the Panel would like.

DR. LEWIS: That would be great. We'll have an opportunity later in the afternoon for that.

DR. GILBERT: Thank you.

DR. LEWIS: Okay, we'll move on.

Dr. McCarthy.

DR. McCARTHY: Thank you. My question is a quick clarification about the endpoint, physical well-being at 1 year. Can you clarify for me, does the 1 year start at the time of mastectomy or does it start at the time of completion of reconstruction? You know, we know that the reconstructive process can take a shorter period of time for someone not undergoing adjuvant therapies, but longer for someone who may undergo both chemo and/or radiation, so I'm looking to understand if we can confirm that everyone at the 1-year mark, for example, had the permanent implant in place.

DR. ASHAR: I'm going to ask Dr. Aguel if he can readily address this question and if not, this will be another item that we can cover after the lunch break.

Dr. Aguel.

DR. ZHAO: This is Yu Zhao from FDA. We believe that is 1 year after the mastectomy.

DR. LEWIS: Okay, thank you.

Dr. Hickerson.

DR. HICKERSON: This is a question that goes back to Integra. Your SurgiMend is very similar to PriMatrix, that a lot of our surgeons have quite a bit of experience with, that is replaced over time, primarily because we don't have the capsule that develops around it

because it's vascularized from underneath and then a graft is applied after it becomes vascularized. So in this situation, have you gone back with the biopsies that you have obtained to look and see the similarity between -- you say that it doesn't change, it's not -- no change within the SurgiMend itself, so that seems a little odd because you've got a good vascular surface that will be above that, that other in-growth could incur from. So I was just curious if you had gone back into any studies to see the comparison then between the collagen changes that are there between the bovine versus the human and with the realization that bovine's going to have a 97% similarity, maybe, within the repeating units.

DR. GILBERT: Thank you, Dr. Hickerson. The studies that were done by Gaster et al in particular, which is the most relevant here, were not done -- Integra had no involvement in those studies and so they were scheduled in tissue expander exchanges. There is data that allows you to see the progression over time, but it's not a pre-specified time course, per se.

I think some of the differences to the PriMatrix scenario that you described, certainly vascularization is an important part of that, but a part of the resorption of the PriMatrix over time also deals with the proteolytic enzymes that are very prevalent in the wound bed that are likely absent or diminished in this setting, particularly in light of the capsule and the tissue integration that occurs.

Having said that, you know, grossly and histologically, the images show very distinguished morphology that is very consistent with the SurgiMend in the breast reconstruction procedures. They did do immunohistochemistry specific for the bovine collagen to confirm that that structure was consistent, was the device -- and so I think that explains part of it. And maybe I stated too strongly earlier, I think what we're seeing is a homeostasis which is not to say that further change is not prohibited. You know, in any tissue in the body you would expect to see some level of turnover of collagen and

replacement with certain malfunctionally viable tissue relative to the local mechanical environment and that may happen slowly over time, but we've not observed at any point for the SurgiMend that it is completely resorbed. And Dr. Adelman, with his clinical experience, would be able to speak to that, as well, if interested.

DR. LEWIS: Yeah, I think we can move ahead.

Dr. Li, you have a question?

DR. LI: Yes, this is really a follow-up on Dr. Ballman's point earlier. One of the problems with the propensity scoring, of course, is that it only takes into account the variables that you know about and along that regard there was a very large discrepancy in the number of ADM patients and non-ADM patients, and I think someone, I forgot who presented, that the non-ADM patients were from 11 different medical centers. So how did those medical centers compare to the medical centers that did the ADM and within -- and can you compare them, say, within -- were there centers that did both ADM and non-ADM so you can compare?

And even if you could get even more granular, was there a surgeon dependence, because there was only a hundred and some odd ADM patients all together, a couple of active surgeons could've done them all, compared to the almost a thousand non-ADM. So can you give us any kind of granularity about these other variables, namely the institution or the surgeon? And you've already said that there was no patient-specific data available, well, all those could be very important distinctions between the groups that are not included at all in the propensity calculations.

DR. LEWIS: Dr. Ashar, can you have someone answer that?

DR. ZHAO: This is Yu Zhao from FDA. Currently, we only have the results of the comparison between the two study groups only based on subjects within the two sites with both the SurgiMend and the control. We currently do not have the baseline comparison

between the two sites with both SurgiMend and control and compared to the other seven sites with only control. And for regarding the surgeon data, FDA did not receive the patient-level surgeon data, so that's the reason why it was not included, any factors related to site or surgeon was not included in the propensity analysis. Thank you.

DR. LEWIS: Dr. Chevray.

DR. CHEVRAY: Yes, I'd like to ask Dr. Adelman with Integra about the randomized controlled trial that was attempted at MD Anderson. Can you tell me, was any part of that trial completed or published anywhere and was SurgiMend one of the ADMs that was included in that study?

DR. ADELMAN: This is Dr. Adelman. Thank you, Dr. Chevray, for that question. Recently, the two arms that we were able to complete, which was a comparison of SurgiMend versus AlloDerm, was recently published and the analysis of that study demonstrated that there was equivalence of the two.

DR. CHEVRAY: Can you tell me who the PI on that study was?

DR. ADELMAN: Off the top of my head, I do not recall. I can look into that.

DR. CHEVRAY: It wasn't you?

DR. ADELMAN: It was not me.

DR. CHEVRAY: Okay.

DR. ADELMAN: Correct.

DR. LEWIS: Dr. Matarasso.

DR. MATARASSO: Thank you very much. This is an extension of an earlier question stream. Please comment on the capsule formation, if there's any difference around the actual implant itself in these patients that had the ADM and if there was -- that's part one. And part two is if there's any capsule noted around the ADM itself.

DR. LEWIS: Dr. Gilbert, it sounds like a question for you.

DR. GILBERT: Thank you. I'm not aware of any analysis that shows details about the capsule around the implant and how it may have changed with regard to the -- we don't see a traditional capsule in the sense of a foreign body response to the SurgiMend device; again, it is a tissue integration process where cells migrate into the surface, into the fenestrations and surface there, as well. There's no foreign body giant cells, minimal inflammatory cells, it really is a vascularized tissue composite structure at that interface.

DR. LEWIS: Dr. Matarasso --

(Cross-talk.)

DR. MATARASSO: Thank you. As a follow up to that, once you went out a year was there -- or sometime in the future, was there any difference in capsular rate versus the control group just in general, on the cohort that had ADM, did they have less or more Baker classification capsules?

DR. GILBERT: The published literature -- I'm sorry, this is Dr. Gilbert again. The publications that we're referring to here do not cover that, those questions, and did not have a no-ADM group, they were limited to evaluation of the SurgiMend population.

DR. MATARASSO: Thank you.

DR. LEWIS: Dr. Roumie.

DR. ROUMIE: Thank you. Christianne Roumie. This question is for the FDA. So in the briefing packet, I'm specifically looking at Table 13, so we will be asked about safety and effectiveness, which you have combined in one clinical kind of outcome. There is much less missing data on the safety aspects; there is much more missing data that had to be imputed on the effectiveness, which is the BREAST-Q. I was wondering whether or not you have a raw analysis without imputation for the BREAST-Q Physical Well-Being score, I did not see that, and the Table 13 shows a proportion. I would like to see kind of the imputed raw means of the score as well as the un-imputed data, if you have that.

DR. ASHAR: Audra, can you address that question on behalf of FDA?

DR. ZHAO: This is Yu Zhao from FDA. So for the BREAST-Q Physical Well-Being (Chest) score, because we -- you know, as we know, the SurgiMend study is based on a subset of the observational study. So without randomization, the two study groups are subject to potential confounding bias, so that's why we need to use propensity score model adjustments to estimate the treatment effect.

So here, in order to do the propensity score adjustment analysis, the propensity model need to be fit without any access to the outcome data. If we're only doing the analysis based on the completers, that means when we're fitting the propensity score model we need to use partial information about the outcome, that means whether the subjects with evaluable BREAST-Q chest score or not. So in that sense we are not able to provide you the propensity score adjusted comparisons between the two study groups regarding the BREAST-Q. If you're only --

DR. ROUMIE: I think that's fine. I think that's fine. I think we would like to see the raw data on the completers to see if it's differential. You have differential missingness in control and your SurgiMend group. The missingness is different in about 10%, so I am not convinced that your imputation follows, you know, missing-at-random rules.

DR. LEWIS: Okay.

DR. ZHAO: So if you want -- so I'm sorry, this is Yu Zhao from FDA. So if you want to have the -- you know, just basically the observed result with a simple direct comparison, which are potentially subject to confounding bias, we can provide to you that result in the afternoon.

DR. LEWIS: Okay.

DR. ROUMIE: I think that would help us with the totality of the evidence.

DR. LEWIS: Good. Dr. Parker, do you have a question? You're muted.

DR. PARKER: Yes, I do. Sorry, I couldn't find the hand raise button. I apologize. My question is about the medical device reportings that were given to us, and I'm also thinking about the safety communication put out by FDA in 2019 about ADMs in general and what this means to the public and healthcare providers as they're thinking about generalized use of ADMs, SurgiMend being one of those.

I recognize the shortcomings of the medical device reporting, but we still heard about 43 of those that relate to this product specifically and I wonder, even though we know the limitations of that voluntary reporting, if you could give us a sense of how many MDRs there were for ADMs in general during that same time period given that you gave us details on 43 related to this specific product.

DR. ASHAR: Yeah, I'll have our FDA colleague who presented the MDR analysis speak to them.

Debbie.

MS. FELLHAUER: Hi, Debbie Fellhauer. The analysis was completed specifically on the SurgiMend device, so there was no comparison between the SurgiMend and other ADMs, as the panel meeting is to identify the safety and effectiveness of this device alone and our discussion today is specific to the SurgiMend PMA. Thank you.

DR. PARKER: So let me give a little follow-up question to that. How would I, as a patient or a caregiver, consider the number, even though it's voluntary reporting, of that number of reports, what does that mean to me? Can you help me with sort of thinking through that given that there was a safety communication in 2019 from the Agency about the use of ADMs and how I should be thinking about that? Thanks.

MS. FELLHAUER: Sorry, I was having trouble finding my mute button. We actually use MDR data to spot trends. We cannot calculate occurrence rates using this data due to the potential for underreporting and again, so the analysis was specific to SurgiMend, there

is no comparison in this MDR analysis.

DR. LEWIS: Okay, seeing no further questions at this time, we will adjourn -- Dr. Bryant, did you have a question?

DR. BRYANT: A quick question. I understand the limitations of --

(Audio feedback.)

DR. BRYANT: -- ask the Sponsor, can they restate the number of procedures that they expected over the time where those 48 MDRs were reported? Maybe they can give us a perspective so we can at least understand the percentages, if you will.

DR. LEWIS: Doctor?

DR. GILBERT: I'm sorry, could you rephrase the question? We had a little bit of technical -- you broke up during the question. Was it the number of cases --

DR. BRYANT: Can you hear me?

DR. LEWIS: Yes, we do.

DR. GILBERT: We can hear you now, yes.

DR. BRYANT: Got it. Yeah, so understanding -- I understand the limitations with just MDR reporting. Do you have a general range of how many procedures were constructed with the product, going with the product over the time frame where those 48 MDRs were actually, understanding again --

(Audio feedback.)

DR. GILBERT: Yeah, absolutely. We don't have a means to get to the specific number of procedures, per se, but we do have knowledge of the number of the SurgiMend PRS devices that were sold during that time frame. I don't have the precise number at my fingertips, but I believe the number is well in excess of 10,000 units over that 14-year period. I could get the exact number for you later today, if that's desired.

DR. BRYANT: The range helps, thank you.

DR. LEWIS: Thank you. I don't see any further questions.

Oh, Dr. McGrath, I see you have a question.

DR. McGRATH: Just another quick follow-up thought on that. I wonder if the FDA, in looking at those 48 cases, made any effort to kind of sort out, since there's two devices here, how many really pertained to the ADM? In other words, a lot of the things that were being reported may have been simply part of the normal constellation of complications that we see with the use of implants. So did you make any effort to sort out which ones seemed to be actually ADM specific?

DR. LEWIS: Ms. Fellhauer.

MS. FELLHAUER: Debbie Fellhauer, thank you. Thank you for your question, Dr. McGrath. The reports were all read individually, the narratives are read through, that gives the most amount of information, but we did look through all of the reports. But again, because of the limitations of the data we are unable to state with absolute certainty that ADM was or wasn't used in a breast reconstruction. It just depends on what comes in the narratives, so we can only analyze and comment on the information that's actually included in the MDR, not what is excluded.

DR. LEWIS: Thank you. We will now adjourn for lunch and I would ask the Panel members not to discuss the topics during lunch among themselves or with anyone else they encounter, but to reserve the discussions for the meeting. We're running a little over scheduled time, so the lunch hour will be 40 minutes rather than 60 minutes, and we will reconvene at 1:00 p.m. sharp, thank you.

(Whereupon, at 12:19 p.m. a lunch recess was taken.)

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

(1:00 p.m.)

It's now 1 o'clock and I would like to resume the Panel meeting. It's now time for our Open Public Hearing portion of the meeting, which will take the next hour. Public attendees are given an opportunity to address the Panel and to present data, information or views relevant to this meeting agenda.

I believe either Candace Nalls or James Swink have an introductory statement to make.

Ms. Nalls.

MS. NALLS: Both the Food and Drug Administration (FDA) and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group'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 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.

DR. LEWIS: Thank you, Ms. Nalls.

I would like to mention to the Panel, before we get started here, that at 2 o'clock we

will have an opportunity, when we begin our deliberations, to hear answers from any questions that were not adequately answered in the clarifying question session earlier this morning. I would ask that the Sponsor also be prepared to respond if there are questions there, and I would ask the panelists to prepare any questions that they felt were unanswered earlier and be prepared to address them at 2 o'clock. The FDA has a number of issues which they did not address before and they're prepared to answer those, too, so we'll begin with that, but we'll also take up any other unanswered questions that the Panel wishes to address.

We'll now move to the public hearing, we have four live public speakers and we have four recorded sessions and we will begin with those. Each speaker will have 5 minutes for presentation and we ask that you restrict your live presentations to that limit because we need to move on to get the rest of the things done today.

We'll begin with Dr. Ian Saldanha, who is principal investigator for the Administration for Healthcare Research and Quality.

DR. SALDANHA: Thank you, Chair. Good afternoon, everyone, thanks for the opportunity to present our findings of our recent systematic review that we did. I'm here from the Brown University Evidence-based Practice Center in Providence.

In terms of my potential financial conflicts of interest, so I don't have any relevant financial conflicts of interest to disclose, but our project team received funding from the Agency for Healthcare Research and Quality to do this review and I'm the principal investigator. But it should be noted that none of my statements today should be construed as any official position of AHRQ or the U.S. DHHS.

I'm here on behalf of the team, we at the Brown University Evidence-based Practice Center, we had clinicians from the Brigham and Women's Hospital in Boston and we received input on this project from AHRQ, the American Society of Plastic Surgeons has

sponsored the project, and a range of experts in the field who served as key informants, technical expert panel members, and an associate editor and peer reviewers who contributed and enriched our report.

So the context of my brief remarks today are of our systematic review and meta-analysis that was designed to inform a clinical practice guideline from ASPS. This review had six key questions, research questions, I'll only be talking about one. In total, the review had a hundred and sixty studies that were included, a full report is available publicly at the AHRQ website at that link and is available for free.

So the research question I'll be focusing on today is Key Question 5 of that report, which is: For adult women undergoing implant-based reconstruction, or IBR, after mastectomy for breast cancer, what are the comparative benefits and harms of doing IBR with human ADMs or without the use of ADMs in the reconstruction procedure?

There are locations of the report where this question has just passed and they are listed here at the bottom.

So what studies did we include? We included randomized trials, if they had at least 10 participants per group; non-randomized comparative studies, either prospective or retrospective, as long as they were sufficiently adjusted, if they had at least 30 participants per group; and case controlled studies, although we did not find case controlled studies.

So I'm going to briefly walk through the methodology that we used, I'm happy to address questions in the Q&A if there's time. We searched for the evidence, the search is current as of March 23rd this year. We screen studies for eligibility and then, as a standard for systematic reviews, we evaluate the quality of the risk of bias in each study and then across studies for each of the outcomes, we evaluate what's known as strength of the evidence, we consist a range of factors including risk of bias, consistency, precision and others in that assessment. Based on that assessment, the evidence is graded as -- along the

spectrum from insufficient all the way to high, and I'm going to use those colors later on and they'll be a legend that you can reference when I summarize the findings. Once we assess the evidence, we, of course, extract data and conduct syntheses, both qualitative and quantitative. Quantitative syntheses are what you would've heard as meta-analyses.

So briefly what did we find? We found a total of 22 studies in our review addressing this question including two randomized controlled trials and 20 nonrandomized comparative studies. Most were conducted in the U.S. or Canada or both, but there are some other countries, as well, and there were a range of sample sizes in each study ranging from 36 to almost 19,000 patients.

So I'm going to talk about results in terms of two kinds of outcomes, one is clinical outcomes, mostly patient-reported outcomes related to well-being and then subsequently, I'm going to talk about complications.

So in terms of clinical outcomes, there were some outcomes for which we found no data and then for the most, for the rest of them, you can see either the results were inconsistent among included studies or there was just one study and based on just having one study, we could not make a conclusion. And so you can see here every -- all the outcomes here, either we found nothing in terms of clinical outcomes or the results were inconsistent to make a conclusion about whether or not ADM makes the results better.

In terms of complications, we found five complications for which we were able to make conclusions. I'm going to briefly show you four meta-analytic figures. The two on this page are the ones where there was an increased risk associated with ADM use in terms of infections where the effect size was 1.56 with that confidence interval on the right and then for implant failure or loss or need for explant surgery, you can see that there was a 1.8, 1.28 adjusted increase effect size.

There were two outcomes for which -- whether or not they used ADMs, there was

comparable risk, you can see here necrosis and seroma, so you can see the confidence intervals comfortably overlapping the value of 1. So I neglected to mention on the previous slide, but as you can see here in the top figure, when -- the four boxes and lines around them represent the estimates from each of the four studies in the breakdown.

Then there was one outcome for which there was comparable risk, but we did not do a meta-analysis because we required studies -- there to be at least three studies with effect size estimates to do a meta-analysis, but the outcome here is unplanned repeat surgeries. For this particular outcome there was comparable risk, but we did not do a meta-analysis. You can see the estimates here comfortably overlapping 1 for the two studies for which we had estimates.

So just very briefly to summarize, I realize I'm throwing a lot of information at you, but this table is supposed to sort of summarize across the findings in the review. So you can see here, clinical outcomes, we really could not make any conclusions, but in terms of complications, there were two that I showed you that had increased risk, that was implant failure or loss and infections, and there were three that had comparable lists that were unplanned repeat surgeries, necrosis, and seroma.

I hope I'm within the 5 minutes, but thank you for your attention. I yield back.

DR. LEWIS: You're at six and a half, but that's okay.

DR. SALDANHA: Sorry about that.

DR. LEWIS: All right, we'll move to the next presentation, Madris Kinard, Device Events.

MS. KINARD-TOMES: I went to share my screen and it said that someone else was still sharing. Okay, wait, I see it now. Okay. Thank you. Are we good?

DR. LEWIS: You're good, go.

MS. KINARD-TOMES: Excellent. So my name is Madris Kinard and I have no conflicts

of interest. Today I wanted to give you a quick background. I previously worked at the FDA, I was a public health analyst, I worked on UDI, which is unique device identification, which I think is kind of a real challenge here today, to identify devices compared to others, and I was also a subject matter expert for adverse event reporting.

So postmarket surveillance considerations today, of course we talked about MDR data, adverse events that are in the MAUDE database. One of the things I wanted to point out is that with this ADM, of course, sometimes the devices are confused with the ADM within the reports and so I wanted to pull it up in a way that we can look at it all together and hopefully make some sense out of it.

The FDA has not provided a unique product code for biologic mesh and so that's something I think would be really important moving forward to help improve the reporting on this type of mesh.

So there are a couple different factors, the unique device identifier is not being used adequately yet, but as I mentioned, we could make use of the product code a little bit better, and I wanted to make a note that a lot of times physicians are reporting to registries and assuming that the FDA reads that data. And as you see today, really, we're only reviewing very specific data, so I think that something like that needs to be very clear.

This is an example of an Allergan smooth silicone gel-filled breast implant report and you see where the arrow is, it's actually talking about AlloDerm, as well. So this is an example of how the data can be confusing and why we may not be looking at the true number of adverse events that we should be.

There were some questions today about how many MDRs there are for all types of ADM and luckily, I had already pulled that together. So here you can see the timeline and how many reports are coming in, and there are approximately 4,000 reports, not just for SurgiMend but all ADM devices.

The patient problems are not always well coded. On the left here, you can see the patient problems, this is for all ADM and the number of times these appear as a coded outcome. So on the left you can see that necrosis, there's 67 times. When I did a search in Device Events, which contains the MAUDE data, on the term necrosis or necrotic, I came up with a hundred and seventy-three reports. So we do need to look also at the narratives and not just the coded problems.

Then I changed the search criteria just for SurgiMend and these are the reported outcomes with the patient problems, codes, and how many times those terms appear in the narrative. There were some cases of tachycardia and pulmonary embolism, the numbers are low, but those are fairly serious events so I wanted to make sure that those stood out today as we looked at some of this data.

There were two adverse event reports I want to point out where surgical teams had decided that they didn't feel that this was a good device to continue using. It's very rare to see reports like this where they say -- you know, it says however, it hasn't convinced the medical staff on the good behavior of the material and its biocompatibility. I look at reports, I've seen hundreds of thousands of reports and I've seen very few like this.

Another one is listed here and the MDR numbers are at the bottom where there were four different surgeons using the device and they determined that they decided to stop using the product because of similar adverse events that they saw across the cases. These are not breast cases I'm citing right now but they are SurgiMend cases and I wanted to point them out because there have been some questions of the Panel today that relate to its use not just for breast reconstruction.

So one of the things that's super important, of course, is informed consent. I do know that there are a lot of patients who go in for breast surgery and don't know that biologic mesh or ADM is used and it's then made very clear that it's very commonly used

with breast implants. So I think that just because it's off-label use doesn't mean that physicians shouldn't be telling patients about it, you know, they're taking on that risk. I mean, you need to let the patients know they're taking on a risk, as well.

The FDA needs to require that ADM is included in informed consent documents. They have been reviewing informed consent for breast implants and I think that since the two are used together that there really should be one document.

I, again, want to reiterate there should be a unique product code to distinguish ADM from other types of mesh, it would make FDA's job easier. Probably everybody who's looking for this data, they'd be able to find it much more easily.

And then, of course, the FDA needs to work with CMS to require the use of UDI in claims forms and EHRs and it needs to be added to the list of high-risk implantable devices, that CMS is going to start requiring the barcode scans of the device. That list has already been put together by the American Hospital Association, but I'd like to see all types of mesh to be added to that, as well.

I hope I made it in my 5 minutes or close to that and if there are any questions later, I'll be on the line to answer.

DR. LEWIS: Thank you.

We'll now move to Diana Zuckerman from the National Center for Health Research.

Ms. Zuckerman, would you begin?

DR. ZUCKERMAN: Fine. Okay, can you hear me?

DR. LEWIS: I can.

DR. ZUCKERMAN: Okay, great. I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Our center is a nonprofit think tank that scrutinizes the safety and effectiveness of medical products and we don't accept funding from companies that make those products. Today I'm speaking from my perspective as a scientist trained in

epidemiology and public health, who left my faculty research director positions at Yale and Harvard to work on health policy issues in Washington D.C. I was responsible for congressional hearings that found that patients and physicians have been harmed when the FDA did not follow the law pertaining to FDA regulation of medical devices. The law states that devices must be reasonably safe and reasonably effective, and when clinical trials are conducted, they're supposed to focus on the product under review, that specific product and specific indication, and are supposed to show that the benefits outweigh the risks.

My main concern today is that you're being asked to make a recommendation based on 37 SurgiMend patients with successful outcomes. I'll explain that and alert in a few minutes.

I generally like real-world data but in this case, the company analyzed a relatively small subset of data from the MROC study, which the FDA notes, "was not designed to evaluate the safety and effectiveness of the SurgiMend ABDM device."

Now, propensity adjustments do help control for confounding variables, but they didn't in this case control for surgeon or site, as FDA and Dr. Li pointed out, and in such a small study, controlling for every variable at once is not possible. The Sponsor compared outcomes in 1 to 2 years of adverse events for only a hundred and nineteen patients with SurgiMend compared to hundreds more patients without ADM.

And a few of the serious shortcomings of the study include, number one, the MROC study did not collect data on which version of the products were used.

Number two, more than two-thirds of the reconstruction patients did not meet the criteria for clinical success in the ADM group or the non-ADM group. And do you really want FDA to approve this product for all reconstruction patients based on only 37 patients with successful outcomes?

Number three, only two facilities included the ADM patients, so we don't know if

those patients are generalizable to most surgeons or most patients.

Number four, complications were only measured for a year or two, which isn't really long enough, given the possible risks.

And number five, the MROC dataset does not include information on systemic symptoms such as rheumatological or neurological symptoms and it provided very limited information on serious adverse events. The reasons for the reoperations, for example, were not provided.

So just a few more points. The data for important outcomes in some cases were just missing. Thirty-four to forty-four percent of the data were missing on some of these variables. The Sponsor did additional analyses that deleted reoperations as a major complication and that kind of data manipulation is really worrisome. Stating that an elective reoperation is not a major complication makes no sense when reconstruction is, itself, an elective operation.

There were no pre-specified hypotheses for secondary endpoints and we agree with the FDA that therefore those secondary endpoints can't be considered and, as we heard from the previous speaker from Device Events, the coding of adverse events for ADMs is missing thousands of adverse events. We can't assume that only 48 adverse events were reported regarding ADMs in breast surgery. The numbers of those reported are much higher and of course, the numbers of those not reported are even higher.

So in conclusion, I agree that the benefits of SurgiMend are in the right direction. It might be beneficial and I hope that it is, but hope is not the same thing as clear, scientific evidence. Patients and their surgeons deserve a better study involving more patients with the exact product and more surgeons doing those surgeries. We shouldn't have to wait for postmarket studies which could be years down the road and which we all know probably won't be able to keep track of most patients for 5 years.

Thank you very much for the opportunity to speak today, I really appreciate your service on this Panel, look forward to hearing the discussion and would be very glad to answer any questions. Thank you.

DR. LEWIS: Thank you.

We'll move to the fourth presenter, Maria Gmitro from the Breast Implant Safety Alliance.

Ms. Gmitro, you can proceed.

MS. GMITRO: Are you able to see my presentation?

DR. LEWIS: Yes.

MS. GMITRO: Good afternoon, my name is Maria Gmitro. I am president and co-founder of Breast Implant Safety Alliance. Thank you for the opportunity to speak today, and I have no conflicts of interest. I am a former educator, patient advocate, and consumer rep, and I'm also director of community outreach and patient advocacy for TrackMy Solutions, an implantable device tracking company, and I'm also working on board certified patient advocate certification. I am not paid by a manufacturer and I also sit on several collaboratives.

Some patients' concerns, in discussing this with patients, many are unaware that ADM was used, what it actually is, that it was off label and not approved for breast surgery, they're unaware that they can report to the FDA if they have complications and if they did report, they only reported the breast implant or expander and did not include ADM. And patients feel that their trust was violated.

The FDA had their recommendation in March of -- March 31st of 2021 and they were asking for -- you were asking for patients to report problems but again, they're just not aware.

Some ADM mesh surveillance concerns. Often, it's reported with another device

such as a breast implant. It's hard to distinguish which is the problem. When patients self-report, they do not know the type of mesh or they do not realize they should even add mesh. It's difficult to track because there is not a UDI or a unique product code, so how accurate is the current data?

I have a statement from Kimberly Bowles, she is a breast cancer survivor and president and founder of Not Putting on a Shirt, a nonprofit advocating for optimal aesthetic flat closure.

"Robust tracking systems for products used in breast reconstruction, particularly for products not FDA approved for this use due to lack of data, must be in place in order to assess the safety and efficacy of that use. It is critical that patients be fully informed of risks that may impact their decision-making process including the risks associated with products like ADM."

And concerns. Patients have been uniformed up until now. Patients would be shocked if SurgiMend ADM is approved despite the lack of data showing benefit. At least two-thirds of the reconstruction patients did not have a positive outcome as measured, whether or not the surgery included an ADM. More data is needed.

Better data is needed before approval. ADM must be included in informed consent. Require better studies/evidence to determine safety and effectiveness of ADM. Need better tracking, require UDI for ADM biologic mesh, and unique product codes for the different types of ADM.

Thank you so much for the opportunity to speak today and represent patients, and I am available for questions. Thank you.

DR. LEWIS: Thank you, Ms. Gmitro.

We'll now move to the prerecorded presentations.

Ms. Nalls, who will be managing that?

MS. NALLS: Those should be playing momentarily.

DR. GABRIEL: Good afternoon, my name is Dr. Allen Gabriel and I'm a board certified plastic surgeon in the state of Washington. I've coauthored numerous articles involving scaffolds and I'm also a co-editor of two textbooks involving breast reconstruction as well as aesthetic breast surgery. I would like to thank the Panel for allowing me to present my real-world experience in breast reconstruction and specifically focusing on the importance of scaffolds for soft tissue support.

Last year in the United States alone, over 137,000 breast reconstructions were performed. As my colleague, Dr. Steven Sigalove, so eloquently presented on the evolution of reconstruction, our real best chance to create a breast shape is during the mastectomy, as you see in these patients with age 21 on the far left and age 50 on the far right. This is also only possible with the close collaboration with our breast surgeons who perform the mastectomies and then for us, it's possible to perform these and achieve these results because of the device's scaffolds and fat grafting process and methods that the FDA has approved over the years and has allowed us to perform these cases.

But it wasn't always the case. In the past, we were deliberate with more aggressive mastectomies where it made it very challenging for us reconstructive surgeons to perform these cases. Even today we're faced with very thin collapse, as you see in this intraoperative photograph, where it's nearly see-through, you can see the light on the other side of the skin. Imagine how complex this reconstruction would be or how complex this would be without having any additional layers in between to support the implant and allow the skin to heal.

With aggressive mastectomies, unfortunately we're faced with complications and those lead to tissue death, as you see on the far left, and skin necrosis due to lack of blood flow, but it also can lead to seroma and eventually infection and lastly, from the continuous

inflammation, to implant exposure. These are extremely challenging cases, these are extremely challenging for us to perform and complete.

Reconstruction without scaffolds has its own complications and these are complex cases where we see, at times, capsular contracture forming and the rippling formation, as well as lack of implant support that can lead to complications.

So what is it like to be a plastic surgeon and be planning a reconstruction? Well, through a team approach with our breast surgeon, we go over the mastectomy and the pocket dissection. We then move forward with choosing the device and specifically, as we go through this process, we focus on the scaffolds and adding for soft tissue support.

Here's an example of a patient who has undergone a mastectomy who now has completed part of the reconstruction with the device that is surrounded by scaffolds for soft tissue support. Every chest wall is different, there is different angulation of the chest wall, and this makes it possible for when the patient lies down, the implant or the device does not fall towards their armpit and does not also move up or move down towards their abdomen. This soft tissue support becomes critical in these reconstructions, especially as we move down to prepectoral reconstruction.

Here's a device in a prepectoral space with no support and you could only imagine how a traumatized skin could possibly even hold this device in place. Therefore, we see these implant-based reconstructions that have complications where no scaffolds were utilized.

So in summary, surgeons have really embraced scaffolds and I personally have been using it since 2006. Our graduating plastic surgery residents are experienced with these scaffolds and we're seeing more breast surgeons from fellowships who are trained to deliver better mastectomy flaps so we can achieve better outcomes for our patients.

You see, the variables are numerous and it's extremely difficult in the real world to

plan a good randomized controlled trial because we know the benefits of both prepectoral reconstruction as well as scaffolds. So trying to randomize and exclude scaffolds in some patients is extremely difficult when we've been utilizing it so much.

Articles don't outline the real-world experience and the articles are sometimes concerning because we will not be able to get all the information, because the bottom line is our goal is to give the patient a sense of closure and for them to be able to complete their cancer journey. That is what we're all here for and that's what we're trying to achieve, and I would like to thank you again for giving me this opportunity to present.

DR. LEWIS: Thank you, Dr. Gabriel.

DR. SIGALOVE: Good morning, I'm Steven Sigalove from Paradise Valley, Arizona. I'm a board certified plastic surgeon specializing in reconstructive and aesthetic breast surgery. It's a pleasure to speak with you this morning on behalf of The Aesthetic Society. Again, I'm a board certified plastic surgeon in Arizona, I'm an internationally recognized speaker, industry consultant, and published author. I specialize in aesthetic and reconstructive breast surgery, and I have numerous publications and textbooks in reconstructive breast surgery.

These are my disclosures. I'm a speaker and consultant with BD/Galatea Surgical, I'm a consultant with Sientra, and a speaker and consultant with 3M. I have a textbook, along with three other surgeons, in prepectoral breast reconstruction.

I cannot stress to you the importance enough of prepectoral reconstruction and thus, use of soft tissue support such as ADMs and meshes. We've gone through an evolution of soft tissue support since the 1970s, where we started with prepectoral or subcutaneous reconstruction, which were fraught with complications because of thin skin flaps, use of fixed-volume implants, and radical mastectomies. Because of significant capsular contractures and other complications, we then went to total muscle coverage.

This is how I learned breast reconstruction when I was a resident. As you can see, the total muscle coverage was extremely tight, extremely painful, and very poor aesthetic outcomes with lack of projection. We then went into what we call partial muscle coverage, which essentially was dividing the pec muscle and allowing it to window-shade a bit, but as you can see from these reconstructions, it really lacked lower pole support and they were fraught with complications such as bottoming out.

Because of this, we then started doing what we call the dual plane breast reconstruction, which is what many plastic surgeons did for many, many years, where we would divide the muscle and use ADM or other supportive structures like P4HB to lower -- to give the reconstructions lower pole support. We did well with these reconstructions cosmetically, they were excellent However, because we were cutting the muscle, they were quite invasive; patients were on morphine PCA with extended hospitalizations following their mastectomies, leading to significant narcotic use.

The other downside of being under the muscle was something known as hyperanimation, which means every time the patients would move their muscles, the implants would jump up and down, which was exceedingly painful, uncomfortable, and unsightly, which led us back to the prepectoral notion of the early 1970s.

However, nowadays in 2021, we have supportive structures such as meshes and ADMs which are obligatory, in my opinion, for use in prepectoral breast reconstruction. We can't do it without it. Pre-pec reconstruction has allowed us to place the implants on top of the muscle in a minimally invasive muscle-sparing fashion. These mastectomies with reconstruction are performed as an outpatient with minimal use of narcotics, our patients go home on NSAIDs, do incredibly well. We're able to get better cosmetic outcomes because we have improved cleavage compared to the dual plane technique, and our patients are incredibly happy. So I can't stress to you the importance enough of being able

to use some type of soft tissue support such as an ADM or P4HB or whatever the material may be, because without it we have higher complications. There are numerous studies showing higher rates of capsular contracture when these products are not used. Additionally, things like exposure, rippling and wrinkling, thin skin flaps, would make it absolutely prohibitory to do prepectoral breast reconstruction without the use of some type of soft tissue support structure such as an ADM or P4HB.

Our patients do beautifully, they have minimal pain, and again, prepectoral breast reconstruction is here to stay. It is now the number one leading form of prosthetic breast reconstruction in the world and I believe that without these additional measures, such as ADM soft tissue support and other scaffolds and meshes, we would not be able to offer our patients prepectoral breast reconstruction in a safe and extremely reproducible fashion.

Dr. Allen Gabriel will be joining me, he will be continuing the discussion on more of the poignant and salient points of use of meshes and scaffolds in the use of prepectoral breast reconstruction. I anxiously await your questions following the discussion. Thank you very much.

DR. SELBER: Good afternoon. My name is Jesse Selber, I'm professor and vice chair and director of clinical research for the Department of Plastic Surgery at MD Anderson Cancer Center, and I want to thank you very much for allowing me to make a public comment on the FDA panel meeting scheduled for October 20th.

My disclosure is that I am a scientific advisor for Integra LifeSciences and this is my only disclosure relevant to this topic.

The purpose of this panel, as I understand it, is to determine if SurgiMend should be approved to conduct a postmarket approval study in implant-based breast reconstruction, and my comments will be brief and aimed at this purpose.

By of way of historical background, the standard of care up until about the

mid-2000s was total submuscular coverage of the expander and implant. The problems that emerged over time using total submuscular coverage was that the implant became superiorly and laterally displaced by the forces of the muscle, the lower pole was constricted by those same forces, and the breast became unnaturally flat in appearance. In addition, the inferior pole skin, which is where most of the breast volume should be, became underutilized again because of the constrictive force of the pec muscle and over time, these problems were found to be unacceptable aesthetically and functionally.

The solution to this problem, which was developed in 2005 by Andy Saltzberg and has been used in the vast majority of breast reconstructions, increasingly so as of late, is to use ADM or acellular dermal matrix as a lower pole support or hammock for the breast and the advantages of this have been many: increased lower pole expansion and support; reduced reconstructive timeline, meaning a shorter period of time in order to accomplish the reconstruction; and vastly improved aesthetics because of the filling out of the lower pole relative to the upper pole.

Now, the analysis at issue here is a retrospective analysis performed on the basis of the MROC study or the Mastectomy Reconstruction Outcomes Consortium. The study was conducted from 2011 to 2016. It is, as far as we know, the highest level of data available on large retrospective ADM cohorts. Most of the techniques used are so relevant in today's discussion and we feel it's the best comparator for current practices.

The results of a comparison between the SurgiMend arm and the no ADM arm for two-stage implant-based breast reconstruction was performed. There were 119 patients in the SurgiMend group and 868 in the control group, and the statistical analysis plan, which was agreed upon by both Integra LifeSciences and the FDA, was to develop a composite endpoint, what we call the CCS. There was a clinical component of this which included having no major complications, and there's a list of relevant complications in the text you

received, and a patient-reported outcome which was return to baseline for physical well-being module of the BREAST-Q. And the long and short of the outcome of this analysis is that the SurgiMend group achieved the clinical endpoint 32.4% of the time while the control group achieved its clinical endpoint only 21.1% of the time. This had a p-value of 0.02, making it statistically significant. And the conclusion that I think we can derive from this is that SurgiMend is safe and effective in use for implant-based breast reconstruction.

Now, I think the voting items for the Panel specifically are: Is SurgiMend safe? I would say the answer to this is yes, the clinical component of the CCS, meaning no major complications, is higher in the SurgiMend group than in the control group.

Is SurgiMend effective? I would say again, yes. The patient-reported outcome component of the CCS, which is return to baseline satisfaction with chest wall, is higher than in control or submuscular group.

And finally, do the benefits outweigh the risks for proposed use? And again, I would say here yes because overall, the CCS is higher, meaning SurgiMend performed better than the control group and the risks seem to be on par or lower than total submuscular coverage. Based on this, the benefits are clear and this is borne out in the fact that the majority of plastic surgeons are using ADM for this purpose in breast reconstruction.

And so again, I would like to thank you for the opportunity to comment during this panel and I wish you luck with your decisions.

MR. PEARCE: Hello, my name is Marc Pearce and I am the president and CEO of the American Association of Tissue Banks, or AATB. AATB is a professional, nonprofit scientific and education organization. AATB is the only national tissue-banking organization in the United States, and its members total more than 120 accredited tissue banks and over 6,000 individual members. These banks recover tissue for more than 58,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants

performed annually in the United States. The overwhelming majority of human tissue distributed for these transplants comes from AATB-accredited tissue banks. Thus my interest today is to help educate you on human tissue, especially as it relates to human acellular dermal matrices, or ADMs. I have no disclosures to declare.

I want to thank the FDA for providing me with this time to talk to you today, and I want to thank the work of the FDA advisors for closely examining key issues related to potential approval of a xenograft ADM for certain breast reconstruction procedures.

I have two main points. First, human ADMs are different from xenograft ADMs and given those differences, we renew our request for a public workshop to discuss the use of human ADMs for breast reconstruction.

Human ADMs offer distinct clinical advantages over xenograft alternatives. For instance, human ADMs do not possess alpha-gal, which may be present in bovine xenografts. Alpha-gal can result in an inflammatory response in human patients.

Human ADMs have a long history of safe use to reinforce damage or inadequate tissue. Human ADMs were first described for use in breast surgery in 2005. Today, nearly 96% of all material used to provide reinforcement of the post-mastectomy flap during breast reconstruction are human, not xenograft, ADMs.

Human ADMs have a different regulatory structure than xenograft ADMs. Human ADMs for soft tissue reinforcement have been appropriately regulated as 361 HCT/P with primary oversight from the FDA's Center for Biologics Evaluation and Research since 2001. Therefore, any action today related to a xenograft ADM should have no bearing on the regulation of human ADMs.

Given the difference between human and xenograft ADMs, we once again request a public workshop to further discuss the regulation of human ADMs for breast reconstruction. A joint CDRH-CBER workshop would be the best next step to address this point. The

purpose of this workshop would be to:

1. have appropriate regulatory stakeholders to ascertain next steps, i.e. have representatives from both CDRH and CBER present;
2. further delineate FDA's regulatory rationale for making any regulatory change to the classification of human ADMs;
3. explain any potential safety concerns related to human ADMs in breast reconstruction;
4. further explore differences in adverse events reporting as it relates to 361 HCT/Ps versus medical devices; and finally,
5. discuss the particularities of the proposed regulatory framework, especially given that human ADMs are utilized in a variety of settings with and without breast implants.

As I have detailed, human ADMs are different from xenograft ADMs. In light of these differences, we request a public workshop to further discuss human ADMs in breast reconstruction.

Thank you again for providing me with time to speak with you today.

DR. LEWIS: All right. We now will begin the panel deliberations and we have at the present time approximately 2 hours set aside for this. This portion is open to public observers, but public attendees may not participate except at the explicit recognition of the Chair. And we ask that all persons who are going to speak identify themselves each time they speak so the transcriptionist will know who they are.

First, we would like to begin with responses to unanswered questions from the morning sessions and I guess I would first ask the Sponsor if they have any comments or responses to questions from the morning that they felt they didn't have a chance to address adequately before.

Yes, Dr. Gilbert.

DR. GILBERT: Yes, this is Dr. Gilbert. We do have slides ready for a few of the comments that were brought up earlier today. One of my colleagues is bringing up the first.

(Pause.)

DR. GILBERT: So this morning we were asked to comment on the durability of the results for the BREAST-Q dataset, given that the primary -- a component of the primary endpoint was 1 year. And so here we have on this table on the right-hand column the Year 1 data and the Year 2 data. Again, as we have discussed, there were no statistical differences between these groups for any of the different domains. You can see, though, as we look at the top line for Physical Well-Being (Chest), that they're very similar results at both Year 1 and Year 2. We can go to the next slide.

We were also asked just to comment on the differences regarding -- with regards to the different major complication rates for the two groups, and I think I had inaccurately stated that we didn't have that information but that is actually included as Table 8-26 in our Executive Summary for more detail, but we've highlighted on the right, in bold, those that where we saw the most relevant differences. Unfortunately, not all of the data is presented here because the number of complications in each of these categories was less than 10 and so for patient confidentially reasons, that data was omitted from the analysis. Or the presentation of the analysis.

However, you can see that again, consistent with what we've discussed thus far, there was a 13.1% difference in all major complications favoring SurgiMend. We had a slightly higher percentage in the SurgiMend group for explantations.

Maybe to clarify a point from the earlier comments, reoperation absolutely was included as one of the complications in the study and again, showed a very favorable -- favorable for the SurgiMend group and this is including the elective revisions, which was

included as the broader definition of reoperations. So that's a 7.7% difference in favor of SurgiMend. We can go to the next slide, as well, for the Gaster article. Does she have it?

We were asked to comment on the changes that occur in the histologic structure of the SurgiMend device over time and as I mentioned, there's limited data from the Gaster study on this. And I apologize, the reference is inaccurate here. This is Gaster et al. that we've referenced in earlier locations.

So we have the data here. On the top is the H&E slides for 4 months and then two images at 9 months, in which case you can see the very dense pink staining is the collagen from the SurgiMend device that is quite consistent, it's maybe a little challenging to see given the difference in magnification in the publication, but the structure is quite similar between the two.

The 9-month time points, you do see slightly more cellular infiltrate in the center image, which again, one of the findings of the article is that amount of cellular infiltration is directly related to the amount of vascularization in the skin flap that was available.

The lower images are sister slides for the above slides, where the green is staining specifically for bovine Type I collagen and so it's immunohistochemical staining that is very specific to the bovine collagen and maybe to make the point further, there's no staining in the area of the native tissue.

The last point that I'd make from this slide, I was asked earlier about differences in the capsule on the cells, the cell morphology along the SurgiMend device versus the native tissue, the native capsule. And so I'll refer you to the upper left corner, for 4 months, that shows the -- over the SurgiMend, actually there are no cells present on the SurgiMend synovium at that 4-month time point. This makes sense as the cell infiltration is going to come from the surrounding vascularized tissue and in this region, the SurgiMend device is going to be opposed to the tissue expander at that point in time.

In contrast, to the left, the arrowhead that is shown, shows the native capsule formation which has the typical hyperplasia that you would expect to see in a capsule around the implant or tissue expander. The article made no comment that there was a difference in that morphology or presentation than what they would've expected to see in the absence of the ADM.

The last piece that we had to come back to, there had been some questions around the number of SurgiMends used relative to the total number of ADMs that were used in totality in the MROC study, and just to -- I'm sure many of the panelists are aware of these articles, but just to bring back to the discussion, two articles that have come from the MROC study that have looked at the usage of ADM was the Sorkin article describing 1,297 patients with two-stage, immediate, implant-based breast reconstruction, in which it was about 50/50% in the MROC, in this data analysis where 655 patients had ADM used versus 642 with no ADM.

Similarly, in the Kumar paper where 1,451 patients were included, slightly different inclusion criteria for these two different studies but again, within the MROC population about 50% with ADM and 50% with no ADM, again, given these specific inclusion criteria. And it can be assumed that subjects with SurgiMend would've been included in either of these analyses.

So I believe that covered the open topics from the earlier sessions. I'd be happy to discuss these further or to take any further questions when appropriate from the Chair.

DR. LEWIS: Thanks very much, Dr. Gilbert.

Dr. Ashar, does the FDA want to respond now to the outstanding questions?

DR. ASHAR: Yes, we're happy to do that, Dr. Lewis.

So to address questions that pertain to comparisons to other ADMs, while the purpose of this panel discussion is to talk about SurgiMend specifically, we understand that

Drs. Parker and Chevray had questions about how this might compare to other ADMs. So I'll have Cynthia Chang speak briefly on FDA's safety communication that partially addresses this question. And then after that, I'll turn to Dr. Felipe Aguel's group. Dr. Ballman had questions about the demographics at Site 1 and 9 to assure that there was an apples-to-apples comparison in looking at the endpoints. Dr. Sandler had questions about radiation and so the team has been working on providing a response to that. And Dr. Roumie had questions related to non-imputed data on the BREAST-Q.

So with that, I'll move to Cynthia Chang and then following her, it will be Dr. Felipe Aguel.

Cynthia.

DR. CHANG: Thank you, Dr. Ashar.

This is Cynthia Chang, FDA. To address the prior questions regarding defenses and outcomes related to different ADMs, I'd just like to briefly note our safety communication from March of this year. In that safety communication, we noted that data analyzed by the FDA and published literature, together, suggests that some ADMs may have higher-risk profiles than others.

Specifically, the FDA's analysis of the MROC study data showed significantly higher major complication rates of explantation, reoperation, and infections in patients with FlexHD and AlloMax brands of ADM 2 years after surgery, when compared to patients who received SurgiMend or AlloDerm brands or no ADM. And for further details, please refer to our public safety communication, the link is in the Executive Summary and on our FDA website. Thank you.

DR. ASHAR: Thank you, Dr. Chang.

Dr. Aguel, can you or a member of your team try and address the questions that were raised by the Panel?

DR. AGUEL: Thank you, Dr. Ashar.

We want to thank the Panel for some very thoughtful questions that the team has been working on in this time leading up to this point in time.

Regarding the baseline demographics for sites where the SurgiMend was used compared to those where the SurgiMend was not used, we are still working on obtaining and validating that information. We will let the Panel know when we have it available. We do have a couple of slides that we'd like to share to address the other questions that were posed and for that, I'd like to turn it over to Dr. Zhao to walk the Panel through the couple of slides that she has put together.

DR. ZHAO: This is Yu Zhao from FDA.

So the first slide is trying to address the question for the BREAST-Q Physical Well-Being (Chest) score results without PS adjustment and then no imputation, so there was no imputation, it's purely based on the observed data. So at baseline, the mean score for SurgiMend is 82 and for control is 81; and at Year 1, the mean score for the SurgiMend is 80 and for the control is 76. So here, the BREAST-Q Physical Well-Being (Chest) score was a range from 0 to 100.

And this slide gives the proportion of subjects with a change of BREAST-Q Physical Well-Being (Chest) score from baseline, higher or equal to negative four points at Year 1, so basically that is for the components in the primary CCS and here, the results reported here are only based on the observed data, no PS adjustment and no data imputation. So here, the proportion of success regarding the BREAST-Q Physical Well-Being (Chest) score in the SurgiMend is 47% and in the control is 45%.

And the requested subgroup analysis of CCS breast by implant type, that is the textured versus non-textured, is not available. Although the data is available, but completing this analysis will require more time than we have today because we need to

work with multiple datasets and need to merge in the analysis validation for all those. So basically, today, we're not able to provide that subgroup analysis. Please note, it is expected that the number will be less than 11 in the SurgiMend group given that the total number of subjects in the SurgiMend group receiving a textured implant is only 16.

And here, this is an analysis of CCS stratified by the radiation. Also, the reported result here, without propensity score adjustment and no data imputation. So for the patient, for the subgroup of patients not receiving the radiation therapy, the observed CCS success rate was 32% in the SurgiMend and 20% in the control, and for the subgroup of patients receiving radiation therapy, the CCS success rates for the SurgiMend was 21% and 11% for the control.

That's what we have right now. Thank you.

(Pause.)

DR. LEWIS: Dr. Ashar, do you have further people to speak?

DR. ASHAR: Sorry, I was having difficulty getting off of mute. At this time, we don't have anything further. We will let the Panel know when the additional analysis is available. And so we're happy to address any questions that you might have at this point related to what we've provided.

DR. LEWIS: Okay. First, I would ask the panelists if there are other questions that they posed this morning that they feel have not been addressed and could be either by the Sponsor or by FDA before we begin open deliberations. So are there any further questions that the panelists want to pose at this time?

Yes, Dr. Hoffman.

DR. HOFFMAN: I had two questions for the surgeons. Probably Dr. Adelman, I would think. Since this is a two-step procedure, this type of reconstruction and sometimes many months elapse between the initial placement of the expander and the permanent implant,

is there ever an issue with this device being sort of stuck or not being able to separate out the expander and basically disrupting it in the process of trying to swap out for the permanent implant? That's the first question.

The second question, which I think there's not going to be an answer to, but clearly if there had been any issue about the anaplastic large cell lymphoma question with this device, we would've heard about it. But I'm also aware that the average time course for when those developed in people with textured implants was like 9 or 10 years. Is there a reason from the standpoint of a chemical makeup or the molecular makeup of this product that should reassure us that that's not something we might anticipate seeing 6 or 8 years from now?

DR. ADELMAN: This is Dr. David Adelman. Thank you for those questions, Dr. Hoffman. To answer the first question, could the SurgiMend be physically attached to the tissue expander, making it challenging to separate the tissue expander and exchange it for an implant, the short answer is no. In most cases the SurgiMend is well integrated with the surrounding capsule and the tissue expander is separate from that capsule. Particularly nowadays, when we switched away from textured tissue expanders to smooth tissue expanders, there's really virtually no interaction with the smooth expander and the capsule of which the SurgiMend is now a part.

So in the small number of cases where SurgiMend may have had challenges integrating with the capsule, it would be free floating or not attached to the tissue expander and in theory could be easily debrided at the time of expander-to-implant exchange. I would argue those are the vast minority of cases and it is not a problem to do the tissue expander-to-implant exchange.

To try to answer your second question, the analyses, to my understanding, regarding ALCL with textured implants, in the analyses where smooth surface implants were

considered where the rate of ALCL was very, very slim to none, many of those patients had ADMs and SurgiMend would have been included amongst those patients. And so the data that do exist suggest that it's really the textured surface of the implant that's driving the ALCL process and likely not the capsule itself.

DR. LEWIS: Dr. Roumie.

DR. GRANT: This is Dr. Grant, I would just ask to comment as well on the last two questions. With smooth tissue expanders currently in use, there's no issues after the implant exchange.

The only other point I'd add about ALCL is that the product in question here, SurgiMend, has been used in many other anatomic areas of the body for, as you heard, over a decade. No association with any problematic conditions like ALCL have been noted in the abdomen or other clinical sites where it's been used. Thank you.

DR. HOFFMAN: Thank you.

DR. LEWIS: Dr. Roumie now, did you have --

DR. ROUMIE: Yes, sorry, it was just a quick -- Christianne Roumie -- a quick follow-up question based on the additional information that the FDA provided on the warning that was issued in this year, it mentioned two brands. My question is related to if these are bovine-derived or human-derived dermal matrices, given my unfamiliarity with the brand names.

DR. ASHAR: Dr. Chang, can you address this?

DR. CHANG: Yes. So this is Cynthia Chang, FDA. The question was about the source of the ADMs that were mentioned in the FDA safety communication. The ADMs that were mentioned were AlloDerm, AlloMax, and FlexHD. I believe the SurgiMend is bovine and the other three are human. Thank you.

DR. LEWIS: Yes, Dr. Parker.

DR. PARKER: I want to understand the lack of UDI, the unique -- the identifier that's been brought up in the public comments and why these don't carry them.

DR. GILBERT: Thank you for the question. You know, just to clarify, the SurgiMend device is compliant with all regulations relative to unique device identification that became active in the last few years, and so there is a unique identifier associated with the device that can be -- with a sticker that can be left with the medical record for tracking in that respect, you know, for information back to Integra, and I think maybe there's additional aspects of that related to whether that can now be utilized as part of the MDR reporting which, now that that is the standard, it would make sense.

DR. LEWIS: Thank you. Dr. Ashar, I have kind of a fundamental question and I'm not exactly sure who on your team would be the most appropriate to address it, but it's a very broad question. It actually was, I think, brought up by Dr. Roumie before lunch, and that relates to effectiveness, because I think the weakest part of the argument for this device is in regard to effectiveness, as Dr. Roumie pointed out, and it seems to me the MROC study has a couple of really fundamental problems.

Number one, it relies on the BREAST-Q score as a substantial measure of effectiveness, but one could argue that the BREAST-Q score is only minimally dependent on the use of the SurgiMend device, that that score is 90 or 95% dependent on the technique that was used for doing the breast reconstruction, on the surgical technique that was used, and on the various variables, size, position, etc., etc., that went into the surgical technique and that the role of the SurgiMend as a small support structure as part of that is not a major part of the operation, it's almost a purely technical decision on the surgeon's part as to how to close that gap, basically. And there's nothing about the BREAST-Q measure that I can see that reflects any aspect of the use of the SurgiMend particularly, it reflects the broad technique they used and undoubtedly, to a great extent, the surgeon's technique and his or

her experience in doing that.

And then a fundamental weakness in the MROC data, as I understand it, is that only two of the nine centers contributed data regarding SurgiMend. The others were entirely control. And so trying to evaluate control satisfaction of the women with their breast result when one set of surgeons did it and with the SurgiMend where a totally different set of surgeons did it and not very many of them, I mean, we don't know how many surgeons were actually involved in those two centers. It could've been as few as four or five.

I mean, the propensity scoring does not address that at all and cannot address that and yet, that is absolutely fundamental to the MROC data, which is what you're basing everything on. It appears to me that that's an incredibly weak argument for effectiveness. And I don't know if that's an answerable question or not, but it really raises a question in my mind of whether this data is valid. It seems to me those are fundamental weaknesses that no amount of statistical manipulation can address.

DR. ASHAR: Yeah. No, thank you, Dr. Lewis. I think that's exactly why we're interested in having the Panel deliberate on safety and effectiveness and benefit versus risk. And the company may have additional information or insight to offer, but you also have excellent expertise on this Panel from plastic surgeons and others who may be able to help the Panel work through that issue.

From a data perspective, we provided all of the data that is available to us with the exception of the one item that the team is working on, but we would truly appreciate your advice on this. It is always challenging with aesthetic devices to assess benefit versus risk and safety and effectiveness, so your advice and direction would be helpful here. Thank you.

DR. LEWIS: Well, I'd have to really rely on the plastic surgeons on the Panel to address this. It's a difficult question. I don't do this surgery, never did, and so I'm unable to

comment, but I would make the analogy, for example, I've done a ton of hernia surgery in my life and this is a little bit like the question of if I have an inguinal hernia with a significant floor defect and I'm evaluating how to deal with the floor defect, I have two basic choices, I can either approximate the transversalis fascia and use endogenous tissue to do that or I can put a piece of mesh in to bridge the gap and the surgical decision about when to do that is very subjective based on the size of the defect, the gap that you have to close, the amount of tension, etc., it's always an intraoperative decision which the surgeon must make.

This isn't exactly the same, but it's actually similar in many ways, it's a technical decision at surgery, and asking the patient to evaluate it and using the patient's postoperative satisfaction as a measure is really a disconnect. The two don't have much to do with each other. And so using that as an effectiveness measure seems to me to miss the mark. And again, I invite the plastic surgeons on the Panel who have obviously done a ton of this, to please comment and help us out here.

Dr. Hickerson, I believe you're first.

DR. HICKERSON: Dr. Lewis, thank you, sir. I think in this situation you're correct in stating that, but on the other hand, when we look at the ADMs overall, I think we've heard that there's an increased incidence of problems. So when we look at SurgiMend, there was a decreased incidence of problems compared to those that did not have any type of ADM, it looked like.

So when we're looking from that standpoint to look for effectiveness, a lot of it goes back to safety because in a breast reconstruction, any problem that you have is going to reflect on the skin and implant itself and how hard it is, is there a lot of dimpling, everything that goes into that, then, comes into the patient satisfaction, if you will. And I believe that all of the patients would love to have that original breast back and it gets to be extremely

difficult, and any type of safety issue you have is going to reflect upon that, then, as you move forward.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: So one question I have is that you're trying to evaluate the effectiveness based on the patient, and so part of it is to say do the patients fare worse, in their perception, having this procedure in this way and obviously, they're not going to relate that to the specific thing.

So the other issue for effectiveness goes to the surgeon's opinion of the benefit of the procedure and in my work with plastic surgeons, that's kind of their deal and even though we're not asking the question of prepectoral reconstruction, that certainly is coming around and the use of the ADMs is a real part of that.

So I think I don't know if the MROC has any data about the surgeon's rationale or what's the surgeon's opinion of appearance, you know, if they had sort of a similar questionnaire for the surgeons as to their opinion of the appearance of the breast and the ease of surgery with the ADM versus not, and I think that could answer that question for us.

DR. LEWIS: Dr. McGrath.

DR. McGRATH: My thoughts. I agree with you, Frank, about the value of the MROC for patient satisfaction, but I really resonate with what Dr. Marilyn Leitch just said. But in a sense, the plastic surgeons have weighed in, Marilyn, 82% of us use the ADM now. We didn't 5, 6, 7, 8 years ago. And I think that you don't need to do a survey of people to ask them what are the advantages if -- well, you could, but I think the fact that people have spoken with their change in technique kind of already addresses that issue, that clearly the surgeons want a good result, this gives a better result.

Two other thoughts. Remember too, that surgeons have been moving away from the use of textured implants for things that we talked about several years ago and the use

of the ADM. And again, this is not so much with the sling but more with a larger piece of ADM around a smooth implant. But clearly, the benefits of stabilizing the implant that the old, more problematic textured implants offered, now get taken care of by using the ADM. So that's an important feature we shouldn't lose sight of.

And the other thing is there may be -- and this has come up with just kind of a couple of comments this morning, but I think this would be worth pursuing further, there may be less capsular contracture when you're using ADMs, and even if it's a small piece in a sling like this, that may not be such a dramatic number but it certainly would be an extraordinarily dramatic number in the subcutaneous position.

So I think that there's other pieces that we haven't called out, that while we may not see that benefit popping up so much from the MROC, it's clearly there in behavioral changes and the other problems that the ADM has solved with breast reconstruction.

DR. LEWIS: Dr. McGrath, before we go on, I'd like to -- I think you've raised an extraordinarily important point that I'd like to expand on a little and perhaps get the other plastic surgeons to weigh in, and I think it comes down to the fact that the issue of effectiveness, which is here being addressed to the patient, is somewhat misplaced. The question of effectiveness is to be addressed through the surgeon. This is a little bit like asking me whether I want to use 2-0 or 4-0 suture to sew something together, we don't want to ask the patient what the right suture is. You know, that's a technical intraoperative decision and this seems to me, although it's not exactly the same, to have those elements.

So your observation that 82% of plastic surgeons are now using this seems like an extraordinarily important observation. And so what it does regarding our debate is it resolves this into a question of two things, one is what's the safety of the device, does it in fact cause complications, and the evidence there actually is better in regard to saying that SurgiMend is better than the control. We unfortunately don't have any data on SurgiMend

versus the other ADMs that are available or even the other prostheses available, that's an unanswered question, but could you say a little more about that? And I invite the other plastic surgeons to do the same.

DR. McGRATH: The only thing I would add to what you just said, though, is you're using another device and the patient must be informed about it. So I think that piece of it is very important --

DR. LEWIS: Yeah.

DR. McGRATH: -- because that does draw the patient into it, so it isn't strictly a surgical decision, the patient would participate in that part of the discussion, also. So I wouldn't lose sight of that. And the fact that it was an off-label device has been -- it's very confusing for the patients, they don't understand the subtleties and I think that needs to be -- that would help if that were a clearer picture in terms of the patient.

DR. LEWIS: Dr. Compagni Portis.

DR. PORTIS: Thank you. Natalie Compagni Portis, Patient Representative. There's so many really important points here and I want to pull some of them apart. I really hear from the surgeons and I want to hear more that most surgeons are now doing this, and it seems clear that there's a clear aesthetic advantage. As a patient rep and a person who had reconstruction pre-use of mesh, I understand personally that there's a difference and in my patients that I work with I see that. And I think none of us want to lose sight of the safety issues, though, and not say well, it's better, patients are happier because they have a better aesthetic response when we really don't know enough about the safety data. Yet.

And I really appreciate the issues, and Dr. McGrath brought this up, that came out in the Open Public Hearing that (1) all mesh is not created equal and we can't lump it all together because there are differences, not just in performance, but we don't know the safety differences. And the other issue that came up that is important is this issue about

fully informed consent. So to your point, Dr. Lewis, yes, patients aren't going to decide which suture to use, what decisions you're going to make intraoperatively, but I think most patients have no clue that there is mesh in their body and they haven't discussed it, they haven't been told about it and so fully informed consent is really, really vital. And it sounds like in some ways -- and again, I want to hear from our surgeons -- that practice has gotten out beyond, you know, if we're doing this off label, out beyond some of the things that we know scientifically and I know it's hard to get the genie back in the bottle, so to speak, but I really strongly urge us to use a precautionary principle here and not grant approval until we really see the results, both of psychological and cytotoxic studies and have long-term data.

Again, many of us have been in this discussion before about implants and we got way out there and then we're like oh, you know, then we have women lining up to tell us about the challenges there. So I think we need strong assurance about the safety, not just of the aesthetic advantages, but of the real safety and to really attend to those issues. So thank you.

DR. LEWIS: Dr. Ballman.

DR. BALLMAN: Yeah, I also struggle with that whole effectiveness concept. I mean, even using the endpoint that they selected, which I agree, I think there should be probably a different endpoint, when a sensitivity analysis was done it was no longer significant and that raises flags. I mean, I don't think there's clear evidence that, on the basis of the MROC that it is effective because of all the different sort of flaws in the design, all the imputation that was done, all of the -- because of a substantial amount of missing data for that effectiveness endpoint, and so I have some real concerns there.

Also, I do want to say that yes, surgeons make decisions and surgeons have voted, but we've had throughout history sort of issues where physicians said no, no, no, this is the right way to do it and when we finally got a clinical trial done, even in difficult situations, it's

been proven that it has not been the right decision. And you know, yes, I mean, surgeons voted and stuff and even though this chest measure probably isn't the right thing, there would be things that could be measured to show that this is more effective. I didn't see any cosmesis sort of data come out on the MROC study. I mean, there has to be some measurable effect that doing this extra device in the body is actually doing benefit. And I'm not saying it doesn't but I'm saying it could be measured and I'm struggling right now with what we're left with, with this particular study, as to whether it's effective.

DR. LEWIS: Dr. McCarthy.

DR. McCARTHY: Thank you. I agree with your comments, Dr. Lewis and Dr. Ballman. I think one of the challenges is when the MROC study was done in 2011 through 2016, the standard of care in breast reconstruction was submuscular tissue expander placement when the ADM of choice was used on the inferior pole, really, as a patch or a sling inferiorly. We have been presented complication data today and limited effectiveness data, in my opinion, on that.

Now we're at a position in time where the standard of care has moved to prepectoral, which is a different operation, there's no muscle involved, and surgeons will choose to wrap the entire tissue expander in ADM or cover it entirely or cover half of it. So it's really changed the operation and that's what I think ADMs have allowed surgeons to do is this newer technique, which is now really becoming standard of care.

And so what we don't now have, though, is that complication data on this prepectoral procedure or effectiveness data. I would submit that breast reconstruction, the whole goal is to satisfy patients and so patient perception of outcome remains a very important outcome variable, but honing right in on the physical well-being is only one small component and frankly, in clinical practice does not remain complete, in my opinion, at 2 years and so we really need to look across the board at patient satisfaction with outcome,

modules of the BREAST-Q, which is really our best well-validated outcomes measure which asks patients how do they like the look of their breast, how do they feel undressed, how do they feel clothed, things that can get at the aesthetic, a patient's perspective of cosmesis, because a surgeon's perception of cosmesis is important, but at the moment we don't have a standardized way to measure that.

DR. LEWIS: Dr. Chevray. You're muted, Dr. Chevray.

DR. CHEVRAY: Thank you. Yeah, Pierre Chevray from Houston, Texas. I'm a plastic surgeon who performs breast surgery and that's the main thrust of my practice and has been for over 20 years. Whether SurgiMend is approved eventually by the FDA or not, there are still going to be many, many surgeons and surgeries done using SurgiMend and ADM for breast reconstruction, that's being done, and whether this is approved or not, that's not going to change, they're just used off label. So kind of to get to my bottom line, I think that the evidence presented today that SurgiMend is safe and effective or that its benefits outweigh its risks, I don't think has been shown.

And as I said, whether it's approved or not, these surgeries are going to continue, so my belief is that a randomized controlled trial should be done and Dr. Adelman said that MD Anderson, he and others at MD Anderson attempted that and they were not able to get patients to agree to potentially be randomized to no ADM. Well, we've seen other studies where there have been 700 patients with no ADM.

I do not use ADM, I have not used ADM in my implant-based reconstructions for 20 years. All surgeons know that we could talk patients into whatever method we really want if we're not truly objective and looking out for their best interests. So I do not believe that a randomized controlled trial cannot be done. Also, I'd like to say that there were a couple of surgeons who spoke today in favor of SurgiMend and other ADMs and for example, Dr. Adelman, over the last 5 years has been paid over $400,000 by Integra. Jesse Selber,

also from MD Anderson, has been paid over $200,000 in the last 5 years by Integra. This is all information that's available on the CMS Open Payments website. Dr. Gabriel, who spoke to us, has been paid $952,000 over the last 5 years by Allergan, the owner of one of the other ADMs. Dr. Sigalove has been paid $510,000 over the last 5 years by Allergan, the maker of another ADM. So I would question the unbiased or how biased or not those opinions are. I think that's all I have to say.

DR. LEWIS: Dr. Matarasso.

DR. MATARASSO: Thank you, Dr. Lewis. I want to start by saying that the comments that have been made by my colleagues, I have no financial interests and furthermore, breast reconstruction is a rather small part of my practice. I'm at a medical school, I teach residents, I'm familiar with this and so on.

The comments that have been made about comparing this to the surgeon choosing to put mesh in during a hernia, about which suture, these are really valid, valid questions. But I want to underscore something that Colleen McCarthy said, that when you look at the presentations and the timeline, you'll notice that surgeons -- and this is perhaps why 82% of them are using ADM -- are going to prepectoral.

I don't know if everybody listening today recognizes that what we're asking to be looked at here is submuscular coverage of the implant where instead of taking some of the muscle from the belly area to cover the implant, we're not taking that and we're putting the ADM there. That's very different than leaving all the muscle down and putting ADM over it. As somebody showed in their wonderful timeline, one of the presenters, that's where plastic surgery, as Colleen pointed out, that's where the evolution has been since 2016. So one is submuscular and one is prepectoral and I believe -- please correct me, Dr. Lewis, if I'm mistaken, what we're looking at today is using this in a submuscular fashion.

DR. LEWIS: That's correct.

DR. MATARASSO: And as my colleague -- right.

DR. LEWIS: That's correct.

DR. MATARASSO: Thank you. And as my colleague before me just pointed out, you know, it's a completely different thought when you're looking at this prepectoral, when there's nothing between you and the skin or the implant and the skin.

So I salute my friends that are showing us the statistical things. I just point the clinical issues out because I think that's very, very important and what Dr. McGrath said about informed consent if we use another device, I also think is very important.

But please, my friends here, keep in mind the picture that we saw early on of the pectoralis muscle, then the ADM below it, and then the implant below all of that versus this sitting on top of the muscle and nothing between that and the skin because that's where plastic surgeons are mostly using this now, in prepectoral reconstruction. And so thank you very much.

DR. LEWIS: Dr. McCarthy. You're muted, Dr. McCarthy.

DR. McCARTHY: I just put my hand down, apologies.

DR. LEWIS: Oh, you need to put your hand down.

Dr. Li.

DR. LI: Yes, thank you. I'll be brief because my points have already been made. I completely agree with Dr. Lewis and Dr. Roumie and actually just about all of the other speakers, that the issue from -- I'm not a surgeon, so I'm evaluating this purely on the information that I was provided and as has been said, I don't believe that the data that was shown actually shows the safety and effectiveness. Dr. Chevray pointed out that, in fact, it probably is possible to do a controlled study and they weren't able to find almost 800 non-ADM patients, there was not any granularity in the data over surgeons or location, and I'll just make one statistical minor point, is that there were so few ADM patients that if you

look at the complication rate, for instance, on the reoperation rate there was 33 with the SurgiMend against 256 of the control, but the difference between them on a percentage basis is only a percent and a half. If you actually made the 33 complications 35 complications, just add two more complications, the SurgiMend actually would have had a higher reoperation rate. So the statistics are really not supportive at all of safety and efficacy. Now, that's different from Dr. McGrath's actual very cogent point that 85% of the surgeons are doing this, anyway. But to me that's a separate question over how the surgeon decides what they should do and whether or not the data supports the safety and efficacy. So at this point I would say, regardless of the surgical decisions, the safety and efficacy data that I've seen does not appear to support this device.

DR. LEWIS: Dr. Compagni Portis.

DR. PORTIS: Yes, thank you. I want to applaud everyone's comments and Dr. Chevray, I really appreciate the things that you brought up, I think they're really essential points. You know, the loss of a breast is hard, from the patient perspective, I can tell you that and as someone said, we can't replace the breast. And so yes, aesthetic satisfaction again matters and for those of you who are very gifted in that -- but we're really tasked with also U.S. physicians doing no harm and we've seen the negative impact on women's health in the past when we have proceeded without a really strong assurance of comprehensive, long-term data on safety and risk and I just don't want us to lose sight of that. I think it really is vital and I don't think we have seen information yet that makes me comfortable that we know enough about that. Thank you.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: So I know that we're evaluating SurgiMend, but the tissue bank group did speak in the public testimony and so sort of the other issue that's brought up is how the decisions that are made today influence the use of other ADMs and what that will mean to

patient care, which I think is what the tissue bank was trying to bring up, that if you have a problem with one, then you may say that creates a negative environment for all ADMs. And so I don't know kind of how we deal with this issue at the present time, so many surgeons are using ADMs, what the decisions today, how they impact that use overall.

DR. LEWIS: Dr. Sandler.

DR. SANDLER: Thank you. Howard Sandler from Cedars-Sinai. Perhaps a slightly different take from some of the opinions that have been expressed. The data that I reviewed in the summary that the FDA sent out was real-world data which, as we all know, is going to be problematic but still potentially acceptable by FDA for clearing devices. And some of the positive features, I think, of the analysis that was done was the quality of the registry, this is an NIH-funded registry from excellent institutions like MSK and MD Anderson and Michigan and others. So in terms of "real-world data," it's probably pretty good quality real-world data even though there's some missing data as I always see in quality of life studies.

But I think that the analysis plan was pre-specified. The FDA statisticians had primary ownership of the data from the MROC. They presented the data with a hypothesis that the device was superior, they tested that hypothesis and given their pre-specified endpoints of lack of complications and no loss of quality of life, which I think is a priori a pretty reasonable way to look at this kind of registry dataset, they showed no safety signals in my view of the data. And I'm not a plastic surgeon, so take everything I say with a grain of salt, but I overall was more positively impressed with the data that FDA gathered and presented to us than maybe some of the others on the call.

DR. LEWIS: Okay. Dr. Ballman, did you have another comment?

DR. BALLMAN: Yeah, I mean, I just want to point out that there were a lot of caveats and we need to keep those in mind. I mean, one thing is that the data were missing at

random for the efficacy endpoint, which obviously is not true because the control arm had more missing data on that endpoint than did the other arm, which brings up factors. The other thing I want to point out is -- and the FDA did say this, but we need to keep this in mind, that they can only adjust for the variables that were collected. That does not guarantee that when a patient sitting in front of a surgeon or when a surgeon makes the decision that it's captured everything that goes into the decision as to why a patient has mesh versus why they do not, so those biases cannot be removed with propensity analyses.

They can be minimized to some extent and that's not always even the case, sometimes it even makes it worse. There have been situations where that has come up. So I just want us to be a bit cautious looking at the data. And then my final point is, is I am very concerned with the short amount of follow-up. We've seen with implants that things don't show up until 5, 6 years and more down the road and we have, at most, 2 years of data in MROC and by 2 years it's getting very scanty in terms of the reporting. So those are just some other observations.

DR. LEWIS: Dr. Roumie.

DR. ROUMIE: Thank you. So Christianne Roumie. I think I appreciate what Dr. Sandler is saying in that the analysis -- I love real-world data, I think it's great, I use it all the time, but I think that the question as it is, is asking us to separate safety and effectiveness. The analysis, the ATT analysis that was done, combines the two and then asks you to make a determination which you shouldn't, really, if you're trying to look at safety and effectiveness separately, right, they're posed as separate questions so you need to review the data separately. So as far as safety, I do think that there's a reasonable amount of data there regarding safety because they did have kind of tracking and less missing data as far as safety. The effectiveness is really the issue because, as our Chair eloquently pointed out, this is so biased and really, the patient perspective of their

satisfaction is so intertwined with their like of the surgeon, what was the operation like, did they have complications. I think it really does go to their surgical procedure and how it was handled and I think that that bias cannot be separated out. And then you're throwing in a quarter of the data is missing and then you're assuming kind of that it's missing at random and then -- I mean, I think there's just so many assumptions in that part of the study that I am just not confident in a lot of those results.

DR. LEWIS: Dr. Parker.

DR. PARKER: So I agree with many of the comments, but I would underscore the concerns about safety. I do not hear sufficient data to support safety or effectiveness from what I've heard presented, sort of underscoring the comments of others, and the lack of that data doesn't allow us to make an assumption that it is safe and that it is effective. And I understand that it's being used in practice and practice guidelines in the practice of medicine and how that's conducted really aren't the purview of the Agency. The Agency is really about letting the public know that this product is safe and effective.

So I think there's a high bar on those and we all agree, a randomized controlled trial is the way to go to garner the kind of data and evidence to support adequate assessment of risk and benefits, and I think it's upon us to continue to hold high standards for that. I understand it may still be used off label, and many things are, but that leads to the next step to adequately communicating with the public, with patients, what it is they're getting on the other side and it's a challenge. If UDIs exist and they're not being used and they're not being tracked and we don't really know what's happening on the other side, the public needs to understand that kind of stuff and it's messy. So I just underscore the need to hold a high bar for assuring that we really are confident if we do say there is safety and efficacy and I have not seen data to support either one of those in the analyses that we've heard so far. Thanks.

DR. LEWIS: Dr. Hickerson.

DR. HICKERSON: Thank you, Dr. Lewis. This is Bill Hickerson, plastic surgeon. The comments are all very interesting, but I think that as we sit back, as plastic surgeons we all realize that we're not created equal. Dr. Lewis, there are some hernia surgeons that I'd go to and some that I wouldn't go to. Obviously --

DR. LEWIS: You're muted, Dr. Hickerson.

DR. HICKERSON: Excuse me. Obviously, from Dr. Chevray's standpoint, he gets excellent results without an ADM. Unfortunately, ADMs have benefited a lot of surgeons to get the results that he may be able to get without it. So with that, I think that they have been a great addition to the breast reconstruction world and obviously, I was not the primary breast reconstructive surgeon but I've done a fair amount.

But that having been said, I think that if we have a post-approval study it would even be beneficial to be able to collect a lot of that data and be able to do so, because I personally think that the safety has been shown and the effectiveness is there based upon a lot of the statements to the fact that it's being used and the decrease in incidence of the problems that occurred in this product versus the overall standpoint.

DR. LEWIS: Thank you.

Ms. Brummert.

MS. BRUMMERT: Pretty much everybody's asked the questions that I've had on my mind, but I do want to say that the PMA process is supposed to have the best data supporting good outcomes for rigorous testing. I haven't seen that yet, so I just kind of want to underscore what a lot of other people were saying. And I also want to say that the surgeons who spoke earlier were more concerned with aesthetics than safety and that's not our job, so I just kind of wanted to pop in about that.

DR. LEWIS: Thank you.

Dr. Chevray.

DR. CHEVRAY: Yes, Pierre Chevray. I wanted to add that in the past, synthesis of data about ADM in breast reconstruction has shown probably not what most people would consider conclusively, but has shown that ADM slightly increases the risk for seroma and infection in breast reconstruction. And the data that was just published in July of this year that Dr. Saldanha presented to us showed that the ADM increases the risk for reconstructive failure or explantation of the implant.

Perhaps SurgiMend is a better type of ADM and the data from the MROC study that was repurposed and massaged, I'll say, for the current results that we have seen today may show that SurgiMend doesn't increase the risk for complications, but I'm not convinced and I think the data is definitely not conclusive. And even if SurgiMend is not approved today or in the near future, it's not going to deprive patients of having ADM used in their breast reconstruction, it's done today and it will continue to be done. So I think the FDA should require more definitive, more convincing evidence that I believe can be obtained to show that ADM does not present a higher risk of complications in breast reconstruction.

DR. LEWIS: Dr. Bryant.

DR. BRYANT: Yeah, LaMont Bryant, Industry Rep.

Dr. Hickerson, kind of responding to your point, do you feel that surgeons are given the appropriate training to be able to leverage ADM?

DR. HICKERSON: Yes, sir.

DR. BRYANT: Okay, thanks. And then the only other thing I would say is as a PMA -- and Dr. Ashar, you can -- but as a PMA, the data that we will be evaluating is specifically for this product but not the entire class or --

DR. LEWIS: That's correct.

DR. BRYANT: Yeah, yeah. I just wanted to make sure that the Panel understands.

DR. LEWIS: It's only for this product.

DR. BRYANT: Yeah, thank you.

DR. LEWIS: I don't see any hands raised and so I interpret that as meaning there's no further discussion that anyone would like to pursue. That being the case, I think I might ask the Sponsor if they have any comments to offer in response to what they've heard here in the panel discussion, and we'd ask the FDA the same thing following the Sponsor's response, after which it seems we might be able to move to the FDA questions.

Does anyone have any other things they would like to comment on before we do that?

(No response.)

DR. LEWIS: If not, then let me go back to Dr. Gilbert and invite any comments he has to offer about this discussion.

DR. GILBERT: Thank you, and I appreciate all of the comments from the Panel. You know, clearly this is a very interesting and challenging topic to cover. I do want to summarize with a few thoughts. You know, I appreciate the comments there towards the end to bring the focus back to SurgiMend PRS ABDM, the product that has been proposed by Integra for this specific indication, for subpectoral, immediate, implant-based breast reconstruction. Prepectoral breast reconstruction is not being considered here from Integra's perspective, nor is other human ADM, so the focus is on our product today.

In trying to establish and what we believe is shown to meet the premarket approval standard for this product, we took a number of things into consideration, one of which was that over the last 6, 7 years the company has been evaluating the opportunity to do a randomized clinical trial and has been frustrated at various levels in that regard. The MROC dataset is probably the pinnacle, the most well-recognized, the most comprehensive dataset available that is relevant to the indication for use for this product. We referred

back to the 2019 Panel, many of which -- many of you panelists were a member of that group and at that time, and as FDA presented, there were a number of criteria that you established as guidelines for what it would take to be considered for approval for this indication and we believe we've met all of those. You know, we appreciate the considerations regarding long-term follow-up and are committed to a post-approval study to do that. However, what we have been communicated was that a minimum of 1-year follow-up would be adequate for consideration and then we, through the MROC data, have provided 2 years of data follow-up when available. Again, some of that was outside of our control. But we utilized the BREAST-Q as the effectiveness measure for this composite endpoint, which I'll come to in a moment.

That is the only validated, qualified metric for evaluating breast reconstruction that, as I said, has actually been qualified by the FDA and the Panel had stated at that point in time that that could be considered as a tool for effectiveness. There are a lot of modules, as you guys -- I'm sorry, I apologize. As the panelists had pointed out, we were particular in choosing the Physical Well-Being (Chest) domain for this evaluation because we really were trying to focus on the impact of the SurgiMend ABDM.

As was pointed out in multiple parts in the discussion, this is a complex procedure with multiple components and it is difficult to isolate the effects of any one of those pieces. And so the Physical Well-Being (Chest) domain looks at problems with the chest, around pain, tenderness, that would be most likely to be impacted by the inclusion of an ADM in a procedure. While we focused on that, you know, if you look at our -- I encourage the Panel to look at Table 8-15 of our Executive Summary which shows the other modules of the BREAST-Q that were all collected in the MROC dataset and all of which, as part of the SurgiMend study, show a directional change in favor of SurgiMend, all of which again help to support the effectiveness of the product. It's unlikely that it would ever be entirely

possible, even in a randomized clinical trial, to isolate the effect of this product on the effectiveness or safety of a component. You know, we believe that we have provided very robust, reliable real-world data to support that point. And we presented superiority in a composite clinical success metric that included and tied together a very rigorous safety profile, our component, where the patients could have no complications in order to be deemed successful. As has been well documented in the published literature, there are adverse events that are known to occur within breast reconstruction surgery in general and so this is a high bar for determining success from a safety component. And again, in order to meet the success of the composite clinical success endpoint there had to be success in both endpoints.

I'll close just by saying that we also should take into consideration, as we stated in our presentation, that while -- just focus back on SurgiMend, there are no other ADMs that are approved for this indication and while I appreciate the statement that if SurgiMend were not approved there would still be options available, none of those products have gone through and presented this level of data with this conclusive of a result in favor of superiority over no ADM.

With that in mind, I really again thank the Panel for your very thoughtful and very serious conversation around this topic and respectfully ask you to strongly consider that this product, based on the data that's been provided through the SurgiMend study, through the broader published literature, would be approvable and we would certainly welcome suggestions for improvements that we could look at in terms of the post-approval study to help alleviate and mitigate your concerns.

DR. LEWIS: Thanks, Dr. Gilbert.

Dr. Ashar, does FDA have some closing remarks?

DR. ASHAR: You know, I think you've heard from the FDA team there on the analysis

that is outstanding, they continue to work on it, but there's -- I'm being told that they are working to confirm that the numbers are accurate and we may or may not have that available for you prior to your need to consider the questions that have been asked of you. If it does become available, we'll certainly let you, but at this time we don't have that information.

DR. LEWIS: Okay.

DR. ASHAR: Again, that was pertaining to the question that Dr. Ballman asked regarding Sites 1 and 9 and their baseline demographics, as well as the information regarding the endpoints that you've already heard. Thank you.

DR. LEWIS: Okay. Can we move ahead with the questions?

DR. ASHAR: FDA has nothing further at this time. Thank you.

DR. LEWIS: No, I understand that. Can we now move ahead with the FDA questions?

DR. ASHAR: Oh. Certainly, yes. Did you need an FDA spokesperson to read through them or --

DR. LEWIS: Yes, I think we do. We need to have them presented on the screen and have someone to present them.

DR. ASHAR: Okay. Dr. Chang.

MR. VEIZIS: I'm sorry, Dr. Ashar, we do have a prerecorded video on the discussion questions. Do you want us to play that?

DR. ASHAR: That would be wonderful, thank you.

MR. VEIZIS: Thanks.

(Video played.)

The Sponsor performed, or plans to perform, nonclinical evaluations including biocompatibility and mechanical testing. In addition, clinical data were provided. Please comment on whether additional animal studies are necessary to address the time course of

product absorption and tissue response to the implanted device when used next to a tissue expander or breast implant.

The Sponsor plans to perform mechanical compatibility testing with a textured tissue expander and a smooth breast implant device. Please comment on whether additional nonclinical studies are necessary to evaluate mechanical compatibility of SurgiMend PRS ABDM with the existing range of tissue expander and breast implant devices.

Does the Advisory Committee believe a post-approval study is needed for the SurgiMend PRS ABDM (if approved)? If a post-approval study is needed, is the proposed post-approval study acceptable? If not, please recommend changes to the proposed post-approval study.

Please note that the requested discussion item related to the proposed post-approval study should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA. The presence of a post-approval study plan or commitment does not alter the requirements for premarket approval and a recommendation from the Panel on whether the benefits of the device outweigh the risks. The premarket data must reach the threshold for providing a reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered.

(Video stopped.)

DR. LEWIS: Okay, is it possible -- I guess the first question basically relates to whether animal studies are indicated relative to histocompatibility of tissues. Do the panelists wish to comment about that?

Dr. McGrath.

DR. McGRATH: Didn't know if you saw me. I don't think that animal studies are indicated, just for the reasons that the presenters made this morning, that because of

lifespan and so forth and so on, but I do think more cytologic studies would be helpful. Since all of these are two-stage procedures, there is an opportunity for additional inquiry into the tissue that's removed at the time that the permanent implant is put in. There really is only one study, the Gaster, that right now looks at the histology and cytology, and I would like to see a little bit more done in that regard.

DR. LEWIS: Thank you.

Dr. Leitch.

DR. LEITCH: I agree that the animal studies are not going to be really informative for the things people sound like they're worried about with respect to this device because we're not going to have "long-term" data relative to those animal studies. As Dr. McGrath pointed out, there is the opportunity to evaluate the histology at the time of exchange of the implant.

Of course, that's going to be at various intervals, but maybe that's good that you -- because there is that differential in time among reconstructions of when it will be done, so that would be an opportunity to get more histologic data about the changes and to see if there are any markers. But obviously there's been long-term data with the device in other sites and so far not indications that there is something unusual. In this case, though, we have an implant in communication with the device, so it's not unreasonable to try to get more histologic data, but from human data more than animal data.

DR. LEWIS: I think the -- well, a lot of comments, Dr. Ashar, but I believe that the feeling of the Committee in general is that this is probably beyond animal data at this point in time and that further animal data would not be a recommendation that we would support.

DR. ASHAR: Thank you, Dr. Lewis.

DR. LEWIS: Could we see Discussion Question 2 again? Would it be possible to show

that or not?

DR. ASHAR: It should be. Let me ask.

DR. LEWIS: I can read it, if you'd like.

Discussion Question 2, to frame it again for you: The Sponsor plans to perform mechanical compatibility testing with a textured tissue expander and a smooth breast implant device. Please comment on whether additional nonclinical studies are necessary to evaluate mechanical compatibility of SurgiMend PRS with the existing range of tissue expander and breast implant devices.

Okay, we can take that question off now. I guess my first comment on this is that given the fact that plastic surgeons are moving away from textured tissue devices, whether expanders or implants, pretty much universally, it would seem to me, as a non-plastic surgeon, that that question is becoming moot. Whether or not it's desirable because of smooth implants is an open question. But could we have comments from the Panel on whether additional nonclinical studies are necessary in regard to this device?

Dr. Leitch.

DR. LEITCH: This is Marilyn Leitch. Again, I would say that the nonclinical studies are probably not going to be too informative on this point, as there is a lot of clinical data about the use in this circumstance, so I would not be inclined to recommend that, I'm more for clinical looks at things rather than animals at this point.

DR. LEWIS: Dr. Li.

DR. LI: I would say that preclinical testing would only be appropriate if we knew what we were testing for. So in the absence of knowing how these devices fail mechanically, which I believe is what the point of preclinical testing would be, in the absence of knowing how they fail, I'm not really sure what test you run or how you determine what the conditions of that test are. So it's not so much that I'm against

preclinical testing, but in the absence of knowing what I'm testing against, I don't know what I would suggest.

DR. LEWIS: Thank you.

Dr. McGrath.

DR. McGRATH: I was just going to comment that, as you pointed out, even as we're moving away from textured tissue expanders, if the Sponsor is going to be doing mechanical compatibility testing, I would do it on smooth tissue expanders and smooth implant devices and the reason for that is that the shell is a little bit different in thickness and composition on the textured versus the smooth and the mechanical features would be maybe quite different and therefore would be more useful with a smooth expander.

DR. LEWIS: Any other panelists have comments?

(No response.)

DR. LEWIS: Seeing none, Dr. Ashar, I believe the consensus is that nonclinical studies again would not be expected to be very rewarding in this instance and that the Panel mostly feels the need to focus on clinical studies of these devices.

DR. ASHAR: Thank you, Dr. Lewis.

DR. LEWIS: The third question is: Does the Advisory Committee believe a post-approval study is needed for the SurgiMend device (if approved)? If a post-approval study is needed, is the proposed study acceptable? If not, please recommend changes.

Comments from the Panel. This is a little bit hard to answer since we haven't fundamentally decided whether it's approvable or not, but Dr. Ballman, could you begin?

DR. BALLMAN: Yes, I do think a post-approval study is necessary. Also, I think there needs to be something in place to ensure that there's at least 90% complete 5-year follow-up data and an obvious stick might be if they can't get that, then approval gets withdrawn or something like that. I don't know how else to sort of make it known that this is a serious

consideration, because we've had these in the past and people just haven't gotten the follow-up. I do clinical trials in cancer and we do get that follow-up, so it is possible. Also, I think that it's going to be hard to know, at the end of the day because it's a single-arm thing, if it's the mesh or if it's the implant that is causing the complication, so I don't know how the FDA figures they're going to be able to sort that out. I didn't see any sort of rationale for why it's a hundred and fifty. It's going to be hard if it's not a homogeneous sort of implant that's being used, there probably isn't going to be enough power or there's no power anyway because they say it's descriptive to understand, you know, if it's due to a particular implant.

I think that the time to the start of adjuvant treatment should be collected because I've been hearing that there might be some delay because of the use of the mesh and again, it's a single-arm trial so that's going to be hard to interpret, but I do think there's historical data out there. And also, I think the RT question, as well, there needs to be something with respect to that. And finally, just given if this is approved, I don't think we have a lot of data on the effectiveness, so I think there needs to be some sort of effectiveness endpoint in there, as well.

DR. LEWIS: Thank you very much.

Dr. Leitch.

DR. LEITCH: Marilyn Leitch. I agree, the study needs to be larger in terms of the number of patients. The follow-up needs to be -- you know, I would say you need 5-year follow-up and the Sponsor asked for some strategies about that. You know, with cancer patients, we do follow those patients and so if the Sponsor would partner with medical oncologists, surgical oncologists, who are routinely following these patients, I mean, when I see my patients in long-term follow-up and they're having complications of reconstruction, I refer them back to the plastic surgeons, so that's an opportunity. Now, you have to pay for

that in the sense of having clinical research associates that can gather the data and that sort of thing, but with cancer patients -- I know reconstructive patients that have plastic surgery for other reasons are often hard to follow, but for cancer patients, they're in a program of follow-up as it stands and you just got to get to the people that are following them and have them have research associates that can administer questionnaires and ask some questions. And I think there are many sites where surgeons do follow their patients in long term, I know I do for at least 5 years after their cancer surgery, so I would be happy to participate in a study like that to get more data for our patients.

DR. LEWIS: Thank you.

Dr. Sandler.

DR. SANDLER: Thank you. Howard Sandler from Cedars-Sinai. I think Dr. Ballman mentioned it, but I'll just add on very briefly that I think in a post-approval study, if one is done, they should -- the study participants or the study organizers should make sure that they capture the radiation question and perhaps, as a secondary or exploratory endpoint, assess whether there's any interaction between the use of mesh and radiation, if that's possible. I'll thank the FDA for gathering data from the MROC study showing that, at least with the small numbers, there was no obvious safety signal with patients who received radiation.

DR. LEWIS: Thank you.

Dr. Hickerson.

DR. HICKERSON: Dr. Lewis, thank you, sir. I agree also with all of the other comments that 5 years, say, would be required. And I think that also during this time period would be the great aspect of collecting the data on any of the adjunct therapy that could be done, and also included within that study could be the biopsies that could be accomplished as it's built into the study to say that you want to do that on the utilization of,

since it's a two-stage, going back and getting your biopsy of the capsule at the time that you put in your permanent implant.

DR. LEWIS: Thank you.

Dr. Roumie.

DR. ROUMIE: I agree with everything that's been said. My one kind of caveat is based on some of the information that we've heard from the plastic surgeons, their study population in the proposed trial would be restricted to the two-stage subpectoral breast reconstruction, which we've heard is becoming out of favor for a prepectoral reconstruction. So I would encourage recruiting both patient populations and then analyzing them potentially together to find the effects of the ADM, as well as separately to see if there's differential effects. But I think again that we need a substantial enough population and they need to be followed for a long enough period of time and given the duration of recruitment and how practices change, I would encourage a wider view of the ADM.

DR. LEWIS: Thank you.

Dr. McCarthy.

DR. McCARTHY: Yes, this is Colleen McCarthy from MSK. I agree with Dr. Roumie, if we're talking about what's going on in the real world, in the real world the trend is definitely to use ADM in prepectoral reconstruction. It is further allowing some surgeons to proceed direct to single stage and so I think the indications or reasons for proceeding with the trial in one or two or three arms should be considered.

DR. LEWIS: Thank you.

Dr. Ashar, I believe the comments indicate that a post-approval study would be recommended and individual panelists have identified for you exactly what they think that study should entail in addition to what was outlined. Does that seem adequate to you?

DR. ASHAR: I have two questions, Dr. Lewis, that we would sincerely appreciate feedback on. The first is, is that the Panel has noted that the practice of medicine is changing with these reconstructions being performed using the implant in a prepectoral position. At the same time, we would like --the panelists think that we should have a control arm. For that circumstance, does the Panel have any specific recommendations regarding the appropriate control? That's question number one.

And question number two is on the topic of endpoints, does the Panel have any specific recommendations related to endpoints in addition to use of BREAST-Q?

DR. LEWIS: Okay, good questions. We need some help from the plastic surgeons, I guess, since everyone's doing this.

Dr. McGrath.

DR. McGRATH: I'm a little bit troubled about if we're talking about a post-approval study, to then put in a piece on prepectoral reconstruction. That's a different operation, it's got different factors, it's got different features, it's a whole constellation of different things and I don't think that belongs in a post-approval follow-up study. I would definitely think that there's value in approaching that at some point, but I think it should be done separately.

And secondly, and this is just a quick comment for Dr. Sandler, with regard to the question of radiotherapy, for many people if there is a belief from the sentinel node biopsy that you're going to need radiation, many of us won't proceed with the implant reconstruction at that time, so it may make it very hard to get a large enough number of patients and I just throw that out there because I think it would take a fairly large cohort to really get meaningful data about that issue. Thank you.

DR. LEWIS: Dr. McCarthy.

DR. McCARTHY: Colleen McCarthy, MSK. To answer Dr. Ashar's questions, the first

question, I would suggest three arms, I would suggest the submuscular, submuscular or subpectoral with ADM assisted, and then the third arm being the prepectoral.

DR. LEWIS: Thank you.

Dr. Roumie.

DR. ROUMIE: Yeah, my question relates to Dr. Ashar's question on endpoints. I would also consider adding, as has been brought up, rheumatologic endpoints for the patient and whether or not there are other rheumatologic conditions that develop post-procedure.

DR. LEWIS: Thank you.

Dr. Sandler.

DR. SANDLER: Thanks, Howard Sandler. Just very, very quickly, I just wanted to say that I understand that the number of radiation patients in a post-approval study may be very low, but if we don't a priori get the data element in the dataset, we might miss the signal if it exists.

DR. LEWIS: Dr. Hoffman.

DR. HOFFMAN: I'm concerned hearing what Dr. McCarthy says and what some of the other plastic surgeons have noted with respect to this. If the world is truly changing substantially toward prepectoral, maybe it's just going to be impossible to accrue enough people for the submuscular one to do a post-marketing analysis, submuscular, and I think that the plastic surgeons seem to be in agreement about that, but perhaps there are still a significant cadre of surgeons who are, in fact, still doing the procedure we've been hearing about today.

DR. LEWIS: Dr. Leitch.

DR. LEITCH: Marilyn Leitch. I think that you also need to have data elements that reflect why the surgeon selected the type of procedure and then their impression of

aesthetic outcome, as well as the patient's impression of aesthetic outcome.

DR. LEWIS: Thank you.

Dr. Hickerson.

DR. HICKERSON: Dr. Hoffman, paradigm shifts within plastic surgeons are also hard to change, so although it's leading that way I imagine you'll still be able to get a significant amount that would occur. Just like for Dr. Chevray, it would take a lot of effort to get him to change, to start using one. For a lot, it will give them a lot to change to subpectoral, to sub -- or prepectoral implant, if you will.

DR. LEWIS: Thank you.

Dr. Ashar, does that answer your two additional questions?

DR. ASHAR: Yes, it does, thank you very much.

DR. LEWIS: It seems that at this point, having no further comments, we'd be ready to move on to the vote and prior to getting to that, I have two things I want to do. One is to ask if there any final comments which either the FDA or the Sponsor wish to offer beyond what they previously did, and the second is I want to ask our specific non-voting members, Ms. Brummert, Dr. Bryant, and Dr. Compagni Portis, if they have additional comments before we vote. So let's go first to the FDA, if you have any further closing comments.

DR. ASHAR: The FDA does not have any further closing comments. Thank you very much for your deliberations.

DR. LEWIS: Thank you.

Dr. Gilbert.

DR. GILBERT: Just a few closing comments. Again, thank you to the Panel for those comments. We'll certainly look forward to taking those into consideration.

One last comment. Again, as you consider your vote, again, in the 2019 panel discussion, I believe it was actually -- the MROC data was actually emphasized by this group

as a potential source of data for real-world evidence and so I ask you to take that into consideration as you're doing your vote. And maybe just, again, a final comment. While we certainly appreciate how the practice of plastic surgery is developing and the frequency of prepectoral breast reconstruction is increasing, again, our understanding as well is that subpectoral breast reconstruction is still quite common, if not maybe still the majority of cases across the United States. And we do look forward to coming back to the FDA in the future to evaluate first an IDE to evaluate the product in a prepectoral reconstruction, but we understand that that would be a new indication and so again, we really would ask -- you know, we just want to emphasize our focus is on SurgiMend PRS ABDM for subpectoral breast reconstruction.

Again, thank you all for all of your attention and your very thoughtful comments.

DR. LEWIS: Thank you, Dr. Gilbert.

I would like to ask next, Ms. Brummert, if you wish to make any closing comments.

MS. BRUMMERT: No, I don't have any further comments, thank you.

DR. LEWIS: Next, Dr. Bryant. Dr. Bryant is the Industry Representative. Do you have anything further to offer?

DR. BRYANT: LaMont Bryant. Nothing specific. I would just say I would love for us to continue to leverage the value of real-world data and real-world evidence in conjunction with clinical data.

DR. LEWIS: Thank you.

Dr. Compagni Portis, who is the Patient Representative, do you have any closing comments?

DR. PORTIS: Thank you. Just to reiterate that I'd like to strongly urge FDA not to approve at this time without having the kind of long-term substantial data that so many of the Panel have discussed today, and to really strongly hold in mind the idea of safety and

err on the side of really understanding the risks and challenges with using this mesh, and to really hold in mind a comment that has come up about truly fully informed consent for patients where ADM is being used. Thank you.

DR. LEWIS: Thank you.

Dr. Ashar or Ms. Nalls, I'd like to now proceed to the voting and it looks like we need an explanation of how that procedure should be conducted and I believe Ms. Nalls may also have some further information to provide to the Panel before the vote. Could we go ahead with that?

MS. NALLS: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications (PMAs) that are filed with the Agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety and effectiveness are as follows:

Safety as defined in 21 C.F.R. Subsection 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness as defined in 21 C.F.R. Subsection 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and

warnings against unsafe use, will provide clinically significant results.

Panel members, we will now begin the voting process. I will read each of the three voting questions. Each of the voting members have received an electronic ballot to respond to. Once I read all three questions, we will tally the votes and read them into the record.

Voting Question 1: Is there reasonable assurance that the SurgiMend PRS ABDM is safe for the proposed Indications for Use?

Please vote now yes, no, or abstain.

(Panel vote.)

MS. NALLS: Voting Question 2 reads as follows: Is there reasonable assurance that the SurgiMend PRS ABDM is effective for the proposed Indications for Use?

Please vote now yes, no, or abstain.

(Panel vote.)

MS. NALLS: The third and final voting question reads as follows: Do the benefits of the SurgiMend PRS ABDM outweigh the risks for the proposed Indications for Use?

Please vote now yes, no, or abstain.

(Panel Vote.)

MS. NALLS: Please give us a moment as we tally and verify the official votes.

DR. McGRATH: I don't know how to vote.

DR. LEITCH: I think --

DR. McGRATH: Where's the vote?

DR. LEITCH: -- we don't know how to vote.

DR. McGRATH: We don't know how to vote.

MR. VEIZIS: Okay, hold on.

UNIDENTIFIED SPEAKER: Look in your e-mail.

MR. VEIZIS: We have gone to break, so we clear. So you should have received an

e-mail with a link that came from Candace.

DR. McGRATH: Okay.

MR. VEIZIS: Okay, we've got time, we're on break now, we're clear from the public webcast.

DR. CHEVRAY: Yes, my e-mail link came a few minutes ago.

MR. VEIZIS: Perfect, yeah.

DR. CHEVRAY: I'm just letting everyone else know.

UNIDENTIFIED SPEAKER: We can already submit it, correct?

DR. LEWIS: I'm not clear. If we're looking at the screen for Zoom, how can we look at the e-mail? Do we minimize it?

MR. VEIZIS: Yeah, you'd have to minimize your -- either use a device, a mobile device or minimize and then go to your e-mails. Let me see how many does, I guess.

(Pause.)

MR. VEIZIS: Okay, there's just two more people that need to vote, we have 10 votes so far and there's 12 voting members.

You are on mute, Dr. McGrath.

DR. McGRATH: I'm sorry, I don't know how to minimize without losing this Zoom call.

MR. VEIZIS: So let me help you there. You should be able to go to the top and go to exit full screen. Top right where it says views.

DR. McGRATH: Oh, yes.

MR. VEIZIS: And exit full screen.

DR. McGRATH: Yes.

MR. VEIZIS: And that should give you a minimize tab.

DR. McGRATH: Yes.

MR. VEIZIS: And then you can minimize and then go your e-mails and click on the link.

DR. McGRATH: Okay, just a minute.

MR. VEIZIS: No, take your time, we're fine.

DR. McGRATH: Oops. I may lose this.

MR. VEIZIS: There are still two people that haven't voted, so I guess yourself and maybe somebody else. I'm just curious, did everyone vote or does anyone have any issues that I can help?

DR. McGRATH: I have not voted.

MR. VEIZIS: Okay. Has anyone else not voted that was supposed to vote?

DR. LEITCH: I haven't yet, I'm just getting the thing up.

MR. VEIZIS: You got it, no problems. We're almost there, we have 11 now, so we just have one more. We leave the most stressful part of the day until the end. Candace is also reviewing as a moderator, so she's going to get the results. As long as we have all the results, then I'll have Dr. Lewis do that count again and we'll go live on the webcast and we'll provide everybody the results.

(Pause.)

MR. VEIZIS: All right, everybody, we have 12 votes, we're all good, no duplicates, everything's good.

Candace, let us know when you want to go live. You should have the results. As you read the results, we'll show graphs, so just let us know before we go live on the webcast.

MS. NALLS: Will do. I'm putting it together right now.

MR. VEIZIS: You got it. Thank you, everybody.

(Tally of votes.)

MS. NALLS: The votes have been captured and I will now read the votes into record.

On Question 1, the Panel vote was seven yes, five no, zero abstain that the data shows reasonable assurance that the SurgiMend PRS ABDM is safe for the proposed Indications for Use.

On Question 2, the Panel vote was five yes, six no, and one abstain that there is reasonable assurance that the SurgiMend PRS ABDM is effective for the proposed Indications for Use.

On Question 3, the Panel vote was five yes, seven no, zero abstain that the benefits of the SurgiMend PRS ABDM outweigh the risks for the proposed Indications for Use.

The three voting questions are now complete.

Dr. Lewis.

DR. LEWIS: Thank you, Ms. Nalls.

The FDA now asks that the Panel members discuss their votes and if you answered no to a question, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer. Please state your name as before so the recording can identify it and how you voted for each question. For the record, we'll go around the table starting with Dr. Leitch.

DR. LEITCH: So I voted -- Marilyn Leitch. So I voted no on Question 1 based on the concerns about the small numbers in the study of those treated with SurgiMend. I am sympathetic with the Sponsor that they used the dataset that was suggested to be the best one and ended up with a small number that makes it difficult to have good robust data about safety. That being said, I think if there were more patients to look at within that study, it would've been more enlightening in that regard.

With effectiveness, I do think that it is effective in the sense that it's -- by the data that we have available, you only suffer some from the small dataset, but the outcomes are certainly no worse and they are better in certain aspects. And in real-world practice in

terms of the frequency with which the device is used, I think, as Dr. McGrath pointed out, they're talking about the effectiveness of the device.

And so do the benefits outweigh the risks for the proposed indications? I said no on this, again based on having a small dataset. If there were a larger dataset, I think that I would be more likely to vote yes on that question.

DR. LEWIS: Are there any changes in those other things I mentioned that would make a difference to you, Dr. Leitch, in any of your no votes? Labeling, restrictions, other controls.

DR. LEITCH: Well, I mean, I spoke my main things or I would -- if I were confident that the postmarket study would run properly, in other words, have that long-term follow-up, I might be willing to change that. You know, approving and then counting on a postmarket study to verify that we made the right decision is only going to be effective if we can be confident that that study will have the long-term follow-up and the MROC study did not -- was not able to do that successfully.

DR. LEWIS: Okay.

DR. LEITCH: So I think if I could have some confidence of that, I would be willing to change my vote.

DR. LEWIS: Thank you.

Can we next hear from Dr. Ballman?

DR. BALLMAN: So I voted on Number 1, the safety, I voted no and the reason is, is I think the follow-up is way too short. I think in the short-term it does appear safe, but I'm concerned about the longer-term effects that might happen and we've seen sort of an issue with implants over time and so that's why I voted no.

I voted no on effectiveness because I have concern about -- I mean, even though the BREAST-Q is a validated endpoint and as well as the complications, it's not validated to put

the two together, so the composite endpoint was not a validated endpoint. Propensity score can only adjust for measured variables and the sensitivity analyses that were done, the endpoint was no longer significant, so I have issues with that. There was differential missing data between the two groups on the BREAST-Q, which again brings in sort of more biases, so it's hard to interpret that result. And I'm not sure about the generalizability of the results because it was only two centers. So this is the reason I voted no on that.

For Number 3 I voted no because I voted no on the previous two, so I didn't see a benefit and I'm not sure that there is lack of a risk.

In respect to can anything be changed in the labeling that would change my answer, the answer is no.

DR. LEWIS: Thank you very much.

Dr. McGrath.

DR. McGRATH: On Question 1 with regard to safety, I voted yes. I do have confidence in the power of the MROC as real-world data, on the safety side especially. Not only does this show there are no red flags at all, but it certainly points toward greater safety than no ADM use in the same situation. No one has mentioned this, but I was particularly surprised and delighted by the fact that the two things that we associate with ADM, seromas and infections, really did not pop up at all and in fact were very good data points on the MROC study. So I felt confident enough with that data, particularly, to vote yes on Number 1.

With regard to Number 2, although I agree that the MROC study doesn't establish the efficacy from the standpoint of a patient, I'm very compelled by the tacit positive regard for the use of ADM in the 60,000 or so cases that are being done every year with it. I don't think -- someone said that plastic surgeons are more interested in aesthetics than safety, I found that very hurtful, I don't think that's true at all. I think that if our patients weren't

doing well from the safety standpoint, the aesthetics standpoint would be irrelevant, so I don't think that's the case. I think that if we are finding that plastic surgeons in general have moved toward the use of ADM, that's because they're perceiving a benefit in the overall picture, which includes all aspects of the patient care.

And obviously, for Question 3, it flows from 1 and 2 and therefore was yes.

DR. LEWIS: Thank you. Any change in labeling or restrictions that would make a difference?

DR. McGRATH: No, I'm happy, I think this treats lots of things that could be put into a postmarket 5-year study, that would be really interesting to focus on. I'd like to see a lot more focus on their questions about capsular contracture because I think there's positive aspects there. And of course for labeling, I agree with the suggestions about labeling that would be straightforward and also the ones that are about informed consent.

DR. LEWIS: Thank you.

Dr. Chevray.

DR. CHEVRAY: I voted no on Question 1. Really, I don't know, SurgiMend may be safe in two-stage submuscular breast reconstruction, but I don't think the data has convinced me of that. One of the main difficulties I have in accepting the data is that I don't know which surgeons did which surgeries, meaning I think we're comparing surgeons who used the SurgiMend to different surgeons who did not, and I think the surgeon is important, is an important variable and I just don't know which surgeons or how many did which type of operation.

I voted no to Question 2. Again, SurgiMend may be effective in this indication, but I just don't know and the data has not convinced me that it is and so therefore, I voted no to Question Number 3.

DR. LEWIS: Any changes in labeling or indications that would matter to you?

DR. CHEVRAY: No.

DR. LEWIS: Thank you.

DR. CHEVRAY: There was a third part of that question about study, no labeling indication and --

DR. LEWIS: Labeling, restrictions on use or other controls.

DR. CHEVRAY: No, no additional comments or suggestions.

DR. LEWIS: Okay, thank you.

Dr. Hickerson.

DR. HICKERSON: Dr. Lewis, I voted yes on all three, very similar to Dr. McGrath.

DR. LEWIS: Thank you.

Dr. Hoffman.

DR. HOFFMAN: I voted yes on all three questions. I agree with the comments of Dr. McGrath, that if the MROC study was felt to be sort of as good as we were going to get and it showed favorable information with respect to safety, I felt that was comforting information.

Efficacy, I think, is hard to assess. I mean, if the point of this mesh, of this product, rather, is to support the implant and apparently it must do that because we're not seeing such a high rate of failures or explantations or something, at least based on that data, and I did find Dr. Gilbert's comment compelling that this is a complex operation and to try to isolate the effect or the impact that the ABDM specifically has on outcomes, I think is difficult. But you know, based on the data that we've seen, acknowledging that we don't necessarily have the long-term data, I still voted yes on the basis on what we have at this point.

DR. LEWIS: Thank you.

Dr. Li.

DR. LI: I voted no on all three questions based completely on the data that was presented. I think I'm repeating myself from earlier comments, but the dataset for the ADMs was very small, a hundred and nineteen, and although they showed some advantages in several of the categories, the advantages were such that two or three patients actually would've flipped the result. The other thing that greatly influenced me was that there was not very much granularity in the analysis of the result and I understand that the Sponsor didn't have full control of the data, but not being able to separate out confounding variables like institutions, physicians, and patient subjectivity basically put a cloud over why things happened the way they were.

We all know of certain institutions that, for whatever reason, have a higher infection rate than others, but some have lower infection rates than others and we just have no idea what was going on there. So with that and the incomplete dataset left me looking at the data saying that maybe it's okay, maybe it isn't, but the data doesn't really steer me one way or the other.

DR. LEWIS: And would changes in labeling, restrictions on use or other controls make a difference in your voting?

DR. LI: It would not. It would not.

DR. LEWIS: Thank you.

Dr. Matarasso.

DR. MATARASSO: Thank you, Dr. Lewis. So I have concerns and I see-sawed back and forth between being concerned experimentally, but clinically found the data less germane. I voted yes on Question 1.

I was the abstention on Question 2. I appreciated the concerns that the statisticians such as Dr. Ballman and others raised and you raised with the MROC study, so I was concerned about that and I abstained on that.

On Question Number 3 I voted yes.

DR. LEWIS: Thank you.

Dr. McCarthy.

DR. McCARTHY: Thank you. I voted yes on the first question. To use someone else's expression, I didn't see any red flags in the real-world data.

I voted no on Question Number 2 and share the concern that the MROC data did not convince me in the setting of two-stage submuscular reconstruction.

And so then it follows that on Question 3 I voted no, as well. And no changes to my votes.

DR. LEWIS: Thank you.

Dr. Parker.

DR. PARKER: I voted no on all three, similar to comments made by others, that basically I felt like there's insufficient data to support the safety, the efficacy and therefore the last question as well, and those relate to sample size, lack of follow-up, missing data points, lack of generalizability, and I do not think labeling or restrictions or other controls would change at this point. Thank you.

DR. LEWIS: Thank you.

Dr. Roumie.

DR. ROUMIE: Christianne Roumie. For Question 1 on safety, I voted yes, actually based on the short-term data that was presented where -- again, based on the short-term data which was up to 2 years and for many FDA studies that we review, safety is based on 12- to 24-week outcomes. So I thought that there was reasonable short-term evidence for safety. However, for Question 2 on effectiveness, I voted no based on the multiple assumptions and biases that actually creep into that analysis and exactly for the same reason that Dr. Hoffman brought up, which is it's a complex operation and you can't really

tease out what is working here. So that leads me to be unable to state that it is an effective device and because of a disconnect between safety and effectiveness, I voted no on Question 3, which really requires both to be positive.

As far as changes in labeling, I have no changes to the labeling of the device, but I would encourage FDA to consider devices such as these be a required part of the informed consent process. It just seems curious to me that it's not.

DR. LEWIS: Thank you.

Dr. Sandler.

DR. SANDLER: Howard Sandler. So I voted yes on all three questions. I thought that the MROC dataset was very good and I thought that the way the analysis of that data was performed was also very good. The analysis plan was pre-specified. They identified patients who did and who did not use ADM, they used a SurgiMend group and a no ADM group. They used a nice propensity analysis to match the patients as best as possible, realizing that in real-world data you're not going to have true randomized subsets. And overall, they convinced me that their superiority hypothesis was met. And so I voted yes for all three questions.

DR. LEWIS: Thank you very much. I want to sincerely thank the Panel for their service today, the time you put in here and your thoughtful evaluation of all of this and your meaningful participation in all of these questions. This was a difficult decision as evidenced by the split votes on all the questions that were offered and the extensive discussion we've had, but I think all of you have done a superb job and I really have enjoyed working with you for the day. I also thank the FDA for all of their efforts, and the Sponsors for the excellent presentation that they had organized this morning to outline things.

Dr. Ashar, do you have final comments for the Panel?

DR. ASHAR: No final comments. Again, thank you, reiterating Dr. Lewis's thanks for

everyone's time and excellent recommendations. Thank you.

DR. LEWIS: Thank you. Then we will consider the devices panel for today adjourned. And again, I thank all of you for your efforts.

(Whereupon, at 4:00 p.m., the meeting was adjourned.)

1

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

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Via Zoom Videoconference

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

TOM BOWMAN

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