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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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CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES PANEL

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March 29, 2018
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

PANEL MEMBERS:

ANDREW A. BREMER, M.D., Ph.D.	Chair
GEORGE GRUNBERGER, M.D.	Voting Member
MARC S. RENDELL, M.D.	Voting Member
KATHLEEN WYNE, M.D.	Voting Member
AVERY TUNG, M.D.	Temporary Voting Member
ROBERT BURR, M.D.	Temporary Voting Member
WALTER KRAFT, M.D.	Temporary Voting Member
EDWARD W. GREGG, Ph.D.	Temporary Voting Member
BARBARA GOLDSMITH, Ph.D.	Temporary Voting Member
GABRIELLA LAKOS, M.D.	Industry Representative
CAROLYN PETERSEN, M.S., M.B.I.	Consumer Representative
ANNA McCOLLISTER-SLIPP	Patient Representative
PATRICIO G. GARCIA, M.P.H., CDR, USPHS	Designated Federal Officer

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

FDA REPRESENTATIVES:

COURTNEY H. LIAS, Ph.D.
Director, Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health

TARA RABIN
Press Contact

FDA PRESENTERS:

JOSHUA M. BALSAM, Ph.D.
Diabetes Branch
Division of Chemistry and Toxicology
Office of In Vitro Diagnostics and Radiological Health

JISUN YI, M.D.
Diabetes Branch
Division of Chemistry and Toxicology
Office of In Vitro Diagnostics and Radiological Health

SPONSOR PRESENTERS:

MUKUL JAIN, Ph.D.
Chief Operating Officer
Senseonics

JEREMY PETTUS, M.D.
Assistant Professor of Medicine
University of California, San Diego

TIMOTHY T. GOODNOW, Ph.D.
President/CEO
Senseonics

E. LYNNE KELLEY, M.D., FACS
Chief Medical Officer
Senseonics

STEVEN JON RUSSELL, M.D., Ph.D.
Associate Professor of Medicine
Harvard Medical School
Massachusetts General Hospital Diabetes Center

SPONSOR ADVISOR:

NICHOLAS FLEISCHER, Ph.D.
Vice President of Clinical Pharmacology and Biopharmaceutics
Weinberg Group

OPEN PUBLIC HEARING SPEAKERS:

MARK CHRISTIANSEN, M.D.
Principal Investigator
U.S. Senseonics trials

JULIA WEDEL
Patient
Berlin, Germany

STEVEN EDELMAN, M.D.
On behalf of Lisa Powell, Patient

KATHARINE BARNARD, Ph.D.
Health Psychologist
United Kingdom

BENNIE JOHNSON
JDRF
On behalf of Randy Schaaf, Patient

TOBIAS SCHULTE
Patient
Bad Vilbel, Germany

JEFF HITCHCOCK
Founder/President
Children with Diabetes

DOROTHEE DEISS, M.D.
Diabetologist
Berlin, Germany

JOSEFIN PALMEN
Patient
Skurup, Sweden

ADAM BROWN
Senior Editor, diaTribe.org
Close Concerns

TIMOTHY S. BAILEY, M.D.
Investigator
U.S. Senseonics trials

JULIA NEESE
Patient
Munich, Germany

MAEVE SERINO
Close Concerns

DANIEL FINAN, Ph.D.
Director of Research
JDRF

LISA LAIRD, RN
Diabetes Educator
And on behalf of the American Association of Diabetes Educators

DANIELLE SHAPIRO, M.D., M.P.H.
National Center for Health Research

THOMAS MORRIS
Patient
Alexandria, Virginia

SETHU REDDY, M.D., M.B.A., FACP, MACE
Central Michigan University College of Medicine
American Association of Clinical Endocrinologists

EDWARD DAMIANO, Ph.D.
Professor of Biomedical Engineering
Boston University
President/CEO
Beta Bionics

JOHN PETTENGILL
Patient
New York, New York

JOHN LABAN
Pharmacist

INDEX

INDEX

INDEX

M E E T I N G

(8:02 a.m.)

DR. BREMER: I would like to call this meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee to order. It is now, for the record, about 8:02.

I'm Dr. Andrew Bremer, the Chair of the Panel, and I'm very honored to be the Chair and very, very pleased to be here. My background is I'm an internist, a pediatrician and pediatric endocrinologist, and currently a medical officer at the NIH. I do have lots of experience with closed systems and diabetes technology as well as artificial pancreas systems. And, again, it's a delight and pleasure and honor to be here.

I note for the record that the voting members present here today constitute a quorum as required by Title 21 of the 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 Senseonics Eversense Continuous Glucose Monitoring System device. And CGMS is also an abbreviation, and you'll see it throughout the day, for continuous glucose monitoring. The issue to be discussed in this meeting is the first proposal to market a novel continuous glucose monitoring device system. The Senseonics Eversense CGM measures patients' glucose concentrations from subcutaneous interstitial fluid, as opposed to self-monitoring blood glucose meters (SMBGs) -- you may see that abbreviation today -- which measure patients' glucose concentrations from capillary blood. The proposed CGM system uses a fluorescence-based measurement technique, requires minor surgery for subcutaneous implantation, and will have a 90-day sensor wear period. The proposed CGM sensor also

includes a drug component, dexamethasone acetate, in order to mitigate negative effects on sensor life from the foreign body response at the sensor insertion site.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at the table to introduce themselves for everyone in the audience and amongst ourselves. So I'll ask that you please state your name, your area of expertise, your position, and affiliation. And I guess, to make things easier for our roundtable, I'll start with Dr. Lias at my left.

DR. LIAS: Thank you. My name is Dr. Courtney Lias. I am the Director of the Division of Chemistry and Toxicology Devices at the Food and Drug Administration.

DR. KRAFT: I'm Walter Kraft. I'm Professor of Pharmacology at Thomas Jefferson University.

DR. BURR: Good morning. Dr. Bob Burr, Cape Cod Healthcare, Falmouth, Massachusetts. I'm an adult diabetologist.

DR. WYNE: Kathleen Wyne. I'm an adult endocrinologist at the Ohio State University.

DR. TUNG: I'm Avery Tung, and I'm a critical care anesthesiologist at the University of Chicago.

DR. GRUNBERGER: Good morning, I'm George Grunberger. I do diabetes for a living in a suburb of Detroit. I'm also a past president of the American Association of Clinical Endocrinologists.

CDR GARCIA: Good morning. My name is Commander Garcia, and I'm the Designated Federal Officer for this meeting today.

DR. GREGG: Good morning, I'm Ed Gregg. My background is in diabetes and chronic disease epidemiology. I lead the Epi and Statistics Branch in the Diabetes Division at CDC.

DR. RENDELL: Marc Rendell, M.D. I'm Medical Director of the Rose Salter Medical

Research Foundation in Newport Beach, California.

DR. GOLDSMITH: Good morning, I'm Dr. Barbara Goldsmith. I'm a professor in the Department of Pathology, Anatomy, and Cell Biology at Thomas Jefferson University. Thank you.

DR. LAKOS: Good morning, I'm Gabriella Lakos. I'm Senior Associate Medical Director at Abbott Hematology. I'm a clinical pathologist by training, and I am the Industry Representative on the Panel.

MS. PETERSEN: Good morning, my name is Carolyn Petersen. My background is in exercise physiology and medical informatics. In my day job, I'm Senior Editor of mayoclinic.org, but I am here today on my own time as the Consumer Representative. The views expressed are my personal views and do not reflect the policy or position of Mayo Clinic.

DR. BREMER: Great. Thank you, Panel. Again, it's an honor to be here with you today.

For members of the audience, first and foremost, can everyone hear okay?

(No audible response.)

DR. BREMER: Perfect, okay. If there does come a time where you can't, please again just fire a piece of paper at me. It wouldn't be the first time.

Also, members of the audience, if you have not already done so, please do sign in at the attendance sheets which are located outside by the doors.

Okay, also my task today is to keep us on track as far as the agenda, which everyone may have. So as we get further along through the morning, if I curtail things, it's not meant to cut you off; it's meant to stay on track so we stay on the printed schedule.

Now, Commander Patricio Garcia is the Designated Federal Officer for the Clinical Chemistry and Clinical Toxicology Devices Panel, and he'll make some introductory remarks.

Patricio.

CDR GARCIA: Thank you. The Food and Drug Administration is convening today's meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and all 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 in 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. Subparagraph 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 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 the purpose of 18 U.S.C. Subparagraph 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 for Senseonics, Incorporated's

novel Eversense Continuous Glucose Monitoring Device System. The proposed CGM system uses a fluorescence-based measurement technique, requires minor surgery for subcutaneous implantation, and will have a 90-day sensor wear period. The proposed CGM sensor also includes a drug component intended to mitigate negative effects on sensor accuracy and sensor life from the foreign body response at the sensor insertion site.

Based on today's agenda, 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. Subparagraph 208.

Dr. Gabriella Lakos is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Abbott Laboratories.

We would like to remind members and consultants that if the discussion involves 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 at the registration table during this meeting and will be included as a part of the official transcript. Thank you.

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

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 to serve as temporary voting members of the Clinical Chemistry and Clinical Toxicology Devices Panel for the duration of this meeting on March 29th, 2018:

Dr. Robert Burr, Dr. Stephen Clement, Dr. Barbara Goldsmith, Dr. Avery Tung.

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

This has been signed by Jeffrey Shuren, M.D., J.D., Director for the Center for Devices and Radiological Health, on March 26th, 2018.

For the duration of the Clinical Chemistry and Clinical Toxicology Devices Panel meeting on March 29th, 2018, Dr. Edward Gregg and Dr. Walter Kraft have been appointed to serve as Temporary Voting Members. For the record, Dr. Gregg serves as a regular Government employee to the Endocrinologic and Metabolic Drug Advisory Committee in the Center for Drug Evaluation and Research; Dr. Kraft as a consultant to the Pharmaceutical Science and Clinical Pharmacology 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 material to be considered at this meeting.

The appointment was authorized by Dr. Rachel Sherman, Principal Deputy Commissioner, on March 15th, 2018.

Before I turn this meeting back over to Dr. Bremer, I have a few general announcements.

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

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Handouts of today's presentations are available at the registration desk.

The press contact for today's meeting is Tara Rabin.

I would like to remind everyone that members of the public and the press are not

permitted in the Panel area, which is the area beyond the speaker podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you'd like to present during today's Open Public Hearing session, please register with Mr. Artair Mallett at the registration desk.

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

Finally, please silence your cell phones and other electronic devices at this time.

Dr. Bremer, I turn this back over to you. Thank you, Chair.

DR. BREMER: Thank you, Commander Garcia.

So now we'll go in order as far as the agenda, to the Division Director's welcome. And I'd like to extend a special welcome to Dr. Courtney Lias. Courtney Lias is Director of the FDA Center for Devices and Radiological Health's Clinical Chemistry and Clinical Toxicology Office, and it will be our pleasure to hear some opening remarks. Thank you, Dr. Lias.

DR. LIAS: Thank you. We really appreciate the ability of the Panel to come and help us with the Senseonics Eversense CGM submission today.

As many of you know, patients with diabetes have really benefited from the availability of new technologies to help them understand how their behavior and their condition affects their lives, and continuous glucose sensors provide the ability for patients to have additional data available to them, as well as information on trends for glucose when it's rising and falling in their bodies. And this has been demonstrated, both anecdotally and through studies, to benefit patients and their care.

Today we have the pleasure of being able to discuss a new type of technology for the detection of glucose as part of a CGM device. Senseonics will be presenting a lot about that technology, and we'll be following up as well with some of the questions that we have for

the Panel discussion today.

So, with that, we have a very full agenda, so I won't keep you with extended introductions, but I extend my gratitude for your ability to come and provide some advice to FDA on this submission. Thank you very much.

DR. BREMER: Thank you, Dr. Lias.

We will now proceed to the Sponsor presentation. Look at that, I've seen it on the page before I turned it. So I would like now to invite the Sponsor to approach the podium.

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

Ongoing, the Sponsor will have 75 minutes to present, and now I turn the floor over to you. Thank you so much.

DR. JAIN: Good morning, my name is Mukul Jain, and I'm the Chief Operating Officer at Senseonics. I want to thank the FDA and the invited Committee members for the opportunity to present the data supporting the Eversense Continuous Glucose Monitoring System.

Let me provide an overview of the Eversense system and detailed agenda for the remainder of our presentation.

The Eversense system has three components: the implantable sensor, the removable transmitter that is worn over the skin, and the mobile application that runs on a handheld device such as a smartphone. Data from the sensor is sent to the transmitter to calculate and analyze glucose readings. These readings are displayed and tracked on the mobile medical application.

The proposed indication for the system is for continually measuring glucose levels in adults with diabetes for the operating life of the sensor. The system provides real-time

glucose readings, glucose trend information, and alerts for the detection and prediction of episodes of low and high blood glucose. The system is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose meters.

Let me begin by providing more information on how each component of the system works.

The sensor is inserted in the upper arm for up to 90 days and measures glucose every 5 minutes. The sensor also has a silicone collar containing 1.75 mg of dexamethasone acetate, which is eluted locally to reduce tissue inflammation around the sensor.

The sensor technology is based on fluorescence, not electrochemistry like other commercially available CGMs. In our system, our transmitter wakes up every 5 minutes and establishes a wireless link with the sensor. The sensor has no battery. The majority of the volume is actually an antenna which enables the wireless communication with the transmitter.

When the sensor is powered, a current is generated that lights an LED. When the LED flashes, it stimulates the fluorescence in the surrounding gel on the sensor. When the glucose is high, the resulting fluorescence is also high. Conversely, low glucose produces low fluorescence. Therefore, we are able to quantify how much glucose is present based on the fluorescence generated. Because the sensor rests in the cylindrical pocket in the arm, glucose readings are stable. This is the foundation for a longer-duration sensor.

The sensor then directly communicates with the transmitter through the skin. The transmitter uses the data from the sensor to calculate the glucose values and trends. It is worn externally or with a sensor and is secured to the skin with a gentle silicone-based adhesive patch that is replaced daily to ensure comfort and minimize skin reactions. The transmitter also vibrates on the body to provide unique alerts and notifications and

employs a rechargeable battery. The transmitter wirelessly sends glucose information to the mobile medical application, which is the software that displays the information on the smartphone. The app notifies and reminds the user to enter calibration data and also provides the option to upload to Senseonics' data management system for storage and viewing at a later time.

The Eversense system ensures safety through use of multiple alerts. The system produces three kinds of alerts: threshold alerts, which identify glucose levels below or above preset values; predictive alerts, which provides an early indication that a glucose alert level is expected to be crossed in the immediate future; and rate-of-change alerts, which identify rising or falling glucose levels that exceed a preset rate of change.

Importantly, the system has multiple ways to inform the user in the event of an alert. Unique to the Eversense system is the transmitter's ability to vibrate and provide haptic alerts very similar to an Apple Watch. It vibrates regardless of whether the mobile medical application is active or in the vicinity and can vibrate in unique patterns differentiating between low and high blood glucose. When the mobile medical application is active, the handheld device generates both an audible alert and a visual message in addition to the transmitter's vibratory alert.

Next, let's look at how the sensor is inserted. Each sensor is inserted and removed by a healthcare provider during a brief office-based procedure using custom insertion tools. The insertion site in the upper arm is anesthetized with lidocaine and disinfected. Then a small incision is made at the site. The blunt dissector is used to create the subcutaneous pocket of the proper length and depth. The sensor is transferred to the subcutaneous pocket by advancing the cannula to appropriate length with the help of guide marks. Then the sensor is placed by retracting the slider. The sensor is now ready for use with the transmitter worn externally over the sensor. After 90 days of use, patients return to the

physician's office to replace the sensor. The physician locates the sensor by palpating the skin and performs a similar procedure to remove the sensor.

The Eversense CGM system received its CE mark in May 2016. Since that time, the Eversense system has become available in 14 countries, and as of February 2018, about 1,700 commercial patients have received nearly 2,400 sensors, with some patients who are currently on their seventh sensor. In the United States, the application for premarket approval was submitted in October 2016.

The Eversense system has been evaluated in multiple clinical studies with a total enrollment of 2,224 patients through February 2018. Initial feasibility studies were started in September 2008 with several studies still ongoing.

Three multicenter studies have been conducted, one in Europe and two in the United States. The PRECISE study was conducted at seven sites in Europe in a total of 81 patients and was the basis of the regulatory approval in Europe. The PRECISE II study was conducted at eight sites in the United States and is the pivotal study for the PMA. A second U.S. study, known as PRECISION, was conducted at three sites in the United States and provides supporting data for the PRECISE II study.

In addition to these completed studies, a patient registry is currently under way in Europe as part of a post-approval commitment to establish the long-term safety of the Eversense system.

The FDA has asked this Committee to consider design changes to the Eversense system since the PRECISE II study. Specifically, these are changes to the transmitter, glucose algorithm, sensor end cap, and the blunt dissector tool. The majority of clinical data was collected without these changes, and we believe that the study results establish that the Eversense system is safe and effective. These tests or design changes are common in medical device manufacturing and are incremental in nature. They represent continuous

improvement in design over the 2 years since completion of the PRECISE II study.

The sensor end cap and the blunt dissector changes were a result of study observations. Therefore, they will be discussed later in our presentation. I will describe the transmitter and the glucose algorithm changes now.

The Gen-2 transmitter was designed to be more ergonomic. It is more than 50% thinner and lighter, more discreet for the user, and water resistant compared to the Gen-1 transmitter. All of these enhancements were made without any change in the functionality and durability, as confirmed by successful completion of verification and validation testing. The data collected on the Gen-2 transmitter in the PRECISION study demonstrated that the system accuracy and reliability was similar to that of the Gen-1 transmitter. Additionally, nearly all of our commercial experience in Europe is with the Gen-2 transmitter.

Senseonics is requesting approval of an update to the glucose calculation algorithm in the transmitter. The software update improves system performance, particularly in the early sensor wear period and in the hypoglycemic range.

Once the sensor is powered, raw fluorescence data is collected in the sensor and is independent of how the data is analyzed and converted to glucose in the transmitter. Therefore, changes to the algorithm will not affect the raw data itself. The data from the PRECISE study in Europe was used to develop the new algorithm, which we refer to as Software 602. The new algorithm was then used to process the U.S. data post hoc for this submission, similar to how other CGM companies have validated new glucose algorithms. A comparison of the results using the old and new software was provided in the briefing materials. As you will see today, the performance of the Eversense system was accurate and reliable with the study software and was improved with the Software 602.

In addition, FDA has also asked the Panel to consider chemical interference and certain elements of sensor accuracy. Later in our presentation, we will provide evidence

that the data collected during study clinic visits, as well as data collected at home between these visits, adequately characterizes the system accuracy over the entire 90-day course of the sensor life. We will also establish the accuracy in the early wear period. Before discussing the chemical interference, I would like to review some of our study results.

The PRECISE II pivotal study demonstrated the accuracy of the sensor with a mean absolute relative difference, or MARD, of 8.5% through 90 days. Across the entire period of sensor use, 87% of readings were within 15% of the reference value. The sensor detected 96% of hypoglycemic and 98% of hyperglycemic excursions with the 10-minute predictive alert turned on. Finally, 91% of sensors functioned for at least 90 days. Importantly, all findings from the PRECISE study are strengthened by very similar results in the supporting PRECISION study.

The clinical studies also demonstrated the safety of the device and of the sensor insertion and removal procedures. There were no device-related serious adverse events and only one procedure-related serious adverse event in clinic and during home use through 90 days post-insertion. There were no unanticipated adverse events during these studies. There were no device- or procedure-related infections and a low rate of adhesive patch skin reactions. Importantly, the reported adverse events were consistent with other CGM systems and subcutaneous implants.

We utilized a comprehensive approach to characterize the safety of repeat sensor use. First, adaptive risk analysis indicated that the potential risks were predictable, were consistent with currently approved CGM systems, and could be successfully mitigated. This analysis suggested that clinical studies of a single insertion per patient could be used to characterize the impact of sensor insertion, 90-day use, removal, and subsequent healing. The clinical study data established the safety of the device and procedures and also confirmed nominal and complete healing soon after sensor removal.

Finally, results from the ongoing European registry, which is about 1,700 patients and as many as seven consecutive sensor cycles, indicate that repeat sensor use is not associated with an increase in type, frequency, or severity of adverse events.

We also performed testing to determine if any substances cause interference with the sensor function. We tested 41 substances based on ISO, FDA, and CLSI guidance documents, as well as those known to be fluorescent or UV absorbing, medications commonly prescribed in the treatment of diabetes, and those with known interference to glucose test devices. Thirty-nine substances were found to have no interfering effects. Two substances, tetracycline and mannitol, were found to interfere with glucose readings.

Based on these findings, we have proposed a contraindication in the label for mannitol as well as for sorbitol, which is chemically similar. We have also proposed a warning to patients that sensor readings may be inaccurate when patients are taking tetracycline.

Listed here are compounds that do not interfere with Eversense function but are known to interfere with currently approved CGM systems. As this technology does not use electrochemistry, it is not subject to electrochemically active agents like acetaminophen.

Here is the agenda for the remainder of our presentation. Dr. Jeremy Pettus will discuss the unmet need among patients with diabetes. Then, Dr. Tim Goodnow will present the design and effectiveness results of our U.S. studies. Dr. Lynne Kelley will review the safety results, our training program, and details of our post-approval study. Finally, Dr. Steven Russell will provide his clinical perspective on the benefits and risks of the Eversense system. We also have additional experts with us today to help answer questions. They have been compensated for their time and travel.

Thank you. I now invite Dr. Pettus to the lectern.

DR. PETTUS: Hello and good morning. My name is Dr. Jeremy Pettus. I'm a

practicing endocrinologist and Assistant Professor of Medicine at the University of California, San Diego, where I'm involved in clinical research, teaching, and patient care. I'm also someone who has been living myself with Type 1 diabetes for the past 25 years. Additionally, I work closely with a patient-oriented organization called Taking Control of Your Diabetes, where I interact with thousands of people really struggling with this condition across our country every year.

Those of us who treat patients with diabetes, we know the clinical utility of CGM. Regular CGM use can improve overall glucose control, which results in lower A1c values; it can increase time spent in a normal glucose range, and it can improve quality of life. Now, these features are not unique to this system we're discussing here today. All CGMs can provide these benefits. So leading diabetes societies, such as the American Diabetes Association, they recognize this, and they support the proper use of CGM for patients with Type 1 diabetes.

However, despite all of these benefits, CGM systems are still surprisingly underutilized. Therefore, it is a clear unmet need to address some of the barriers to CGM adoption and to get this technology in the hands of individuals who can benefit from it the most.

Now, let me illustrate the utility of CGM with an example. Each of the four dots shown here represent a glucose value taken with a home blood glucose meter over a 24-hour period, and these values would suggest very good diabetes control as they all fall, you know, within the target range between 70 and 180 mg/dL, which is shaded here in gray. However, when we look at the additional data from this patient's CGM, we see there are periods of unnoticed high glucose, shaded here in yellow, and periods of unnoticed low glucose, shown in red. These excursions were not captured with finger sticks alone. So CGM dramatically increases the amount of information available to the patient and to the

healthcare provider with up to 288 values every single day. They provide the level of detail needed to achieve tight glucose control safely.

Now, the greatest benefit is observed in patients that use CGM more frequently. In a study of over 300 patients instructed to use CGM daily, their actual CGM use varied, and as shown on the right here, the largest improvement in A1c is seen in patients who used their CGM system at least 6 days a week.

Now, CGM also protects against severe hypoglycemia, which can be a life-threatening situation. Here, we see the rates of hypoglycemia drawn from two studies, one where CGM was not used and a second where CGM was used. So, without a CGM to alert patients about dropping glucose values, patients with an A1c of approximately 7% will experience one severe hypoglycemic event every 19 months. However, when CGM is worn, that rate drops dramatically down to one event every 60 months or one every 5 years.

But as I mentioned, CGM systems are still underutilized. So the data shown here are from the Type 1 Diabetes Exchange registry, which is a collection of data on nearly 30,000 patients with Type 1 diabetes seen in premier clinics across the United States. So, among patients enrolled between 2010 and 2012, only 7% of patients were using CGM. And from 2015 to 2107, while that rate did increase to 24%, it still means that 76% of patients, or the overwhelming majority of people living with Type 1 diabetes, are still not using CGM.

And in the minority of people that actually do start on CGM, 27% discontinue their use within a year due to a variety of reasons shown here; 61% of patients had problems with the adhesive or with the insertion itself; and another 41% thought the CGM was uncomfortable to use. So this research identifies issues that, once addressed, will promote greater adoption and adherence of this useful technology.

So I believe we need to address the barriers to CGM initiation and continuation and provide patients with choices. We need a system with a longer sensor life so that patients

have to replace their sensors less frequently. Currently approved sensors must be replaced at least twice a month, resulting in 25 to 50 sensor insertions and removals each year. The longer sensor life can reduce this number substantially and may offset some of the discomfort, insertion, and adhesive issues that are commonly cited.

An ideal CGM system would also have a transmitter that's easy to wear and easy to remove whenever desired, without disturbing the sensor, such as during periods of physical activity or when the patient just prefers discretion. I believe this would be an attractive option for patients or for some patients who, at times, would prefer their diabetes to be "less visible."

And the natural evolution of sensor technology is a sensor that is longer lasting and less intrusive. In the 19 years since CGMs first arrived on the market, we've seen their proven clinical benefit. Yet many patients have not adopted the technology or quickly abandon it.

Now, I frequently say that CGM is the one advancement in the 20-plus years since I was diagnosed that has made the biggest positive impact on my life. I hear the same sentiment constantly from my own patients and from those I meet traveling across the country with Taking Control of Your Diabetes. But, unfortunately, I also hear people who have opted to not start on a CGM for one reason or another, or they've tried the device in the past and now have stopped. So I firmly believe we need more CGM options on the market for patients to have access to this potentially lifesaving device.

Thank you. And I'll now turn the lectern over to Dr. Tim Goodnow.

DR. GOODNOW: Thank you, Dr. Pettus.

I'm Tim Goodnow, Chief Executive Officer of Senseonics, and I will present the study design and effectiveness results of the Eversense CGM system. As we mentioned in our introduction, the Eversense sensor has been studied in multiple prospective clinical studies.

These studies include a total of more than 2,200 participants through early February 2018. Today I will present the study design and effectiveness results of the two U.S. studies known as PRECISE II and PRECISION.

As is common in all CGM studies, these studies were designed to focus on characterizing the analytical accuracy of glucose measurement throughout the entire sensor life. Let me begin with PRECISE II, a 90-day study conducted in 90 participants at eight clinical sites.

PRECISE II was a nonrandomized, single-arm, multicenter study; 75 participants had one sensor inserted, and 15 had two sensors inserted, one in each arm. Those with two sensors were evaluated for within-participant precision and for any compression impact on the sensor while sleeping directly on the transmitter. During the study, users calibrated their sensors using a home blood glucose meter. Due to the investigational nature of the system, glucose readings, as well as high and low alerts, were blinded during this study.

Accuracy was measured during daylong clinic visits with blood taken every 15 minutes. This increased to every 5 minutes during hyper- and hypoglycemic challenges. These visits occurred on Days 1, 30, 60, and 90. At each visit, sensor accuracy was evaluated relative to a standard laboratory analyzer known as the YSI. Glucose readings were compared at the same moment in time between the reference analyzer and the continuous device.

On Days 30, 60, and 90, participants also underwent hypoglycemic and hyperglycemic challenges to investigate glucose extremes, as well as upper arm exercise sessions to evaluate the effect of arm motion on sensor performance. Blood glucose reference readings were also taken every 5 minutes during these challenges. A safety follow-up visit occurred at Day 100 or 10 days after the sensor was removed.

The primary endpoint was based upon a measure of sensor accuracy known as mean

absolute relative difference, or MARD. It compares the glucose reading from the sensor with the corresponding reference glucose taken at the same time. A smaller MARD value represents lower error in sensor readings and therefore higher accuracy.

An additional accuracy metric is the percent of sensors that fall within 15 mg/dL or 15% of the reference value. This measure is important because MARD, while a commonly reported aggregate accuracy metric, is an average across all sensor readings and glucose levels. The 15/15 metric, as it is known, is able to add another perspective on accuracy.

Additional effectiveness characterizations are provided to evaluate system accuracy. These include sensor performance across the 90 days of use, agreement of sensor readings within preset accuracy limits such as the 15/15 metric, performance of high and low glucose alerts, the impact of compression, paired precision, analysis of sensor life, and multiple correlative statistical analyses.

The key enrollment criteria for the study included adults diagnosed with diabetes for at least 1 year. Participants could not have had severe hypoglycemia or have had an episode of diabetic ketoacidosis requiring hospitalization within the previous 6 months. The sample of 90 people was representative of the target population for sensor use. The study population was just more than half male with a mean age of 45 years. The mean BMI for the group was 29 with an HbA1c of 7.6%. On average, participants had been diagnosed with diabetes for 20 years. Two-thirds of the sample had Type 1 diabetes, half were using an insulin pump, and one-quarter were using multiple daily injections.

A total of 114 people were consented for the study, and 90 were enrolled. The most common reason for screen failure was unstable cardiovascular status, such as uncontrolled hypertension or symptomatic coronary artery disease. Seven participants were withdrawn prior to insertion as the enrollment limit had already been met. After Day 1, one person was lost to follow-up. During the course of the study, two withdrew consent. One

withdrew consent due to difficulty with the continued IV access required for the YSI testing, and another withdrew due to repeated scheduling conflicts. Five participants received a sensor replacement alert, which ended glucose data collection prior to Day 90. Eighty-two completed the Day 90 visit.

Now let's turn to the effectiveness results. The primary effectiveness endpoint was met using the study software. The analysis was based on all evaluable data in the study, totaling more than 15,000 paired values from all participants with at least one paired glucose reading between the sensor and the reference values. The average absolute relative difference was 8.8%, representing a clinically meaningful accuracy performance. The upper limit of the 95% confidence interval is 9.4%, suggesting that the overall accuracy of the Eversense sensor is materially below 10%.

As mentioned earlier, the algorithm that calculates glucose values was updated after the completion of the PRECISE II study. When we applied the Software 602 algorithm to the raw data, the sensor obtained in the PRECISE II study, the primary endpoint was again met and the MARD improved to 8.5%. Because we are requesting approval for the system using its updated algorithm, all further results in my presentation will be based on Software 602.

The study demonstrated that the system was also accurate across the full 90 days of sensor use. Here we see that 87% of the sensor readings are within 15/15 of the reference. On Day 1, 77% of the readings were within range. Note that reduced accuracy on Day 1 has been seen with other CGM systems and is due to the body's early tissue response to the sensor insertion. Following Day 1, sensor performance improved to 91% and remained stable at 85% or higher at each evaluation time point.

During the course of the PMA review, the FDA requested additional data on sensor accuracy early in the sensor life prior to Day 30, as well as additional observations in the hypoglycemic range; therefore, the PRECISION study was added. The study was designed to

provide greater resolution by adding these two clinic visits and to add additional data in the low blood sugar range.

The design is similar to the PRECISE II study except for the following elements: PRECISION studied 35 people at three sites, 27 of whom had two sensors and started using both the Gen-1 and Gen-2 transmitters. This gave us an opportunity to compare both generations of the transmitter side by side in the same person. Based on the results of the PRECISE II study, the sensor glucose values were unblinded, as were the high and low alerts for this study. The PRECISION results confirm that the sensor is accurate at all measured time points. Sensor accuracy does further improve following Day 1 and remained steady through the Day 90 time point. Importantly, accuracy throughout the sensor life closely matches that seen in the PRECISE II study. This demonstrates a link between the two studies and further strengthens the conclusion that the sensor is accurate throughout the entire life of the sensor.

In characterizing sensor performance, it is customary to evaluate the sensor's accuracy during the beginning, middle, and end of sensor life. Since Eversense is designed to last 90 days, we have evaluated performance at the beginning, at the end, and in between at Days 7, 14, 30, and 60. We believe that this adequately characterizes the performance across the life of the sensor.

Let's look at Day 1 first. These data demonstrate that the Eversense performance is near 80% on Day 1, which is clinically acceptable for continuous monitoring. This is also consistent with all other commercially available systems. Let's put this in perspective. An inherent advantage of a longer-term sensor is that the user experiences only a single Day 1 every 90 days. In contrast, those wearing shorter-term sensors experience up to 12 Day 1's every 90 days. Looking beyond Day 1, Eversense performance reaches the mid-80s and is maintained for the remainder of the sensor life. Similar stable performance is seen after

Day 1 with other systems.

These conclusions are based on six clinic visits spread throughout the sensor's life. Senseonics strongly believes that these clinic visits involving up to 16 hours of blood draws provides good characterization of the system's accuracy. However, to better understand Eversense between Days 1 and 7, we used home blood glucose values as a relative comparator. With this evaluation, we found no deterioration between Days 1 to 7 and, in fact, showed continuous improvement during that period.

Now, let's review the performance of the alerts. In characterizing this performance, the Eversense system was accurate in detecting both high and low glucose episodes. In the PRECISE II study, 96% of low reference values were detected with a false alert rate of 16%, and 98% of high reference values were detected with a false alert rate of 7%. In the PRECISION study, which was designed to include additional observations in the hypoglycemic range, the rates were 95% of low reference values that were detected and an 8% false alert rate. As well, 99% of high reference values were detected with a 7% false alert rate.

The PRECISE II study demonstrated Eversense sensor longevity as well. The Kaplan-Meier estimate of the 90-day survival probability was 91% for PRECISE II. All sensors that did not reach Day 90 produced a sensor replacement alert at the appropriate time. On the right we show the Kaplan-Meier for the PRECISION study, in which all sensors functioned through the entire 90 days. Not only did most sensors last the full 90 days, but participants also wore the transmitters essentially the entire day for the 3-month period. Both studies had an identical median wear time of 23.4 hours per day. Additionally, 87% of the users in PRECISE II and 91% of those in the PRECISION wore the system for more than 20 hours per day, which equates to the 6 days per week that was referenced earlier.

The data demonstrate the high usability of the long-term implantable sensor. And as

Dr. Pettus showed earlier, we know that those who wear the CGM system consistently can benefit the most.

Furthermore, in the clinical study, there was no difference in system reliability between the Gen-1 and Gen-2 transmitter. Across all days of wear in both PRECISE II and PRECISION, system reliability was high, 96% or greater.

Taken in total, the results of both studies demonstrate that the Eversense CGM system produces accurate glucose values throughout the 90 days of sensor life.

The performance of the Eversense system was accurate and reliable with the study software and was improved with the Software 602.

In PRECISE II and PRECISION, 87% and 85% of readings were within the 15/15 of the reference values respectively. Importantly, high accuracy was maintained across the life of the sensor.

There is no degradation of sensor performance near the end of the life, since the system will produce a sensor replacement alert before producing inaccurate results.

Large sensor inaccuracies were relatively uncommon, and glycemic excursions were detected at a high rate.

Finally, both generations of the transmitter design had high system reliability.

These results support the conclusion that the Eversense CGM is an effective continuous glucose monitoring system.

Thank you. I'd now like to turn the lectern over to Dr. Lynne Kelley to present the safety results.

DR. KELLEY: Thank you, Dr. Goodnow.

My name is Lynne Kelley, and I'm the Chief Medical Officer at Senseonics. I will be reviewing the safety profile for the Eversense sensor. In my presentation, I will demonstrate that the Eversense system has an acceptable safety profile that is similar to

other marketed CGM systems; that the procedure risks of an implanted sensor have been mitigated through device design, training, and continued improvements based upon postmarket surveillance; and that the Eversense system actually reduces some of the known risks associated with other CGM systems. I will start with the safety outcomes of the two U.S. studies.

In PRECISE II, a total of 106 sensors were inserted into 90 patients. In PRECISION, 62 sensors were inserted into 35 patients. Counting both insertions and removals, there were a total of 212 procedures in PRECISE II and 124 in PRECISION.

Sensors were used for an average of 92 days, resulting in a total of 9,773 days of in vivo sensor exposure in the PRECISE II study and 6,148 days in the PRECISION study.

The primary safety endpoint in both studies was the incidence of serious adverse events that were adjudicated by an independent medical reviewer, as related to the device or insertion removal procedure. All related adverse events were followed through to resolution.

I will also present results on the incidence of non-serious device- or procedure-related adverse events, adverse events of special interest such as infection or skin reactions and exposure to dexamethasone, the anti-inflammatory contained in a drug-eluting sensor collar.

In PRECISE II, there were no device-related serious adverse events. There was one procedure-related serious adverse event after the investigator was unable to remove the sensor. The investigator engaged a surgeon who removed the sensor without difficulty. However, the surgeon decided to use general anesthesia instead of local, resulting in a serious adjudication.

In the PRECISION study, there were no serious adverse events related to the device insertion or removal procedure. There were three unrelated serious adverse events of

gastroenteritis, a hypoglycemic episode, and cellulitis of the left foot.

A total of 14 device- or procedure-related adverse events were reported in seven patients in the PRECISE II study, and 8 events reported in five patients in the PRECISION study. The majority of transient adverse events were related to the insertion and removal procedure, and most patients in the PRECISION study had two sensors, resulting in four procedures.

The most common adverse events were for pain or discomfort, bruising and erythema. A majority were self-limited, short in duration, and without the requirement for any intervention. Two adverse events were related to the possible retention of a fragment of the sensor casing after removal. Let me provide additional details on these two events.

As part of the protocol, all removed sensors were returned to the Sponsor for inspection. Upon return, two devices were missing a cap. Immediately, a corrective and preventive action was implemented, establishing a process improvement in a cap adhesion step to ensure improved, consistent, high-quality manufacturing. We have modified the end cap design to further mitigate this issue, which I will discuss a little later in my presentation.

It is important to note that the small translucent cap is part of the sensor casing and made of poly(methyl-methacrylate), a well-known and tested biocompatible material that has been used in orthopedic, dental, and ophthalmologic implants. The cap is 3.2 mm by 0.8 mm, which is about half the length of a grain of rice. Due to the small size of the fragment, the high degree of biocompatibility, and the uncertainty that it was retained, the investigators determined that there was no need to attempt to explore the prior incision. The patients were made aware of the adverse event.

With respect to the additional safety outcomes, there were no infections reported in either the PRECISE II or the PRECISION studies. There were no unanticipated adverse

events. All adverse events related to the device or procedure were considered expected for a subcutaneous implant. Importantly, all related adverse events fully resolved.

As mentioned earlier, one of the components of the implanted sensor is a silicone collar impregnated with 1.75 mg of dexamethasone acetate, the same formulation that has been used in other implanted devices to reduce inflammation. This is a water insoluble corticosteroid that acts locally to reduce the body's normal inflammatory response to a foreign body.

The dexamethasone acetate in the collar undergoes controlled release with less than 3 µg delivered per day and less than 300 µg delivered over the entire sensor's life to the local tissue. For context, the average dose of dexamethasone acetate for inflammatory conditions injected into a joint is about 15 to 30 times this amount and is often repeated every 90 days.

Blood draws were performed at baseline, at multiple times during the study, and at study completion. Plasma dexamethasone levels were measured to a very sensitive level with a standard validated assay. No detectable levels were observed at any time point in patients with one sensor.

The dexamethasone collars were also examined after removal, which confirmed that patients had exposure to a maximum of 3 µg per day over the course of the study.

There was one patient with two sensors in the PRECISION study who had transient discoloration of the skin above the sensors. This resolved completely soon after the removal of the sensors.

Now, let's look at the integrated safety results. In an effort to ensure that we have shared with you the entire safety data from all three studies, we have created an integrated safety summary pool. Given a similar population and procedures, the three multicenter studies were included in the pool for a total of 206 subjects, 335 sensors, and 670 insertion

and removal procedures. This pool includes more than 22,000 patient-days of sensor wear. Across all three studies, a total of 41 device- or procedure-related events were reported in 26 subjects or 13% of the study sample.

We took an all-inclusive approach to classifying adverse events such that even short-term discomfort or bruising after placement was recorded when the patient reported the issue. The most frequent events were pain or discomfort and redness. Again, the vast majority were self-limited without the requirement for any intervention.

There were four instances in three patients where a second procedure was required to remove the sensor. This represents less than 1% of the removal procedures.

All three infections in the integrated pool occurred in the PRECISE EU study. Two of the three infections occurred within days following insertion or removal, and the third was an infection of an ingrown hair that occurred as a result of shaving the area just prior to insertion and was separate from the incision. Only one of these required a short course of antibiotics, and none required sensor removal.

We improved incision care instructions between PRECISE and PRECISE II studies, instructing patients to leave the bandage on for 48 hours instead of 24 before changing it. This is the time frame necessary in the healing process to create a water-tight seal in a protected incision environment. I would like to emphasize that this is still a low-rate of infection as compared to literature reports, which is between 2 to 4% for similar implants and minor skin procedures.

Next, let's move on to a European patient registry that Senseonics is conducting to supplement the integrated safety data with information on long-term safety and repeat insertions. This registry includes all who have been inserted in a commercial setting in Europe. As of February of this year, 1,686 patients have been enrolled, and 443 have undergone repeat sensor insertions. All enrolled patients will be followed through eight

insertions and removals.

The low rate of adverse events observed in the U.S. and EU studies is consistent with what we have seen in this registry. As this registry includes all patients who have been inserted with the device to date, we are confident that this is a true representation of potential adverse events.

The most common event was infection, which at less than 1% is below what would be expected for similar minor skin procedures. The second most common adverse event was the need for a second attempt to remove the sensor. We believe this may be related to sensor placement. While this rate is still very low, we've identified a design change to the blunt dissector tool that can further mitigate this risk, in addition to our comprehensive training program.

For the entire European registry, there have been 14 procedure-related infections in 12 patients, all related to the insertion procedure. Several have resolved with a short course of oral antibiotics, and the remainder had the sensor removed without difficulty. Importantly, commercial experience with repeat insertions did not reveal any new safety concerns.

During pre-submission discussions with the FDA, it was determined that the long-term safety of the sensor would be confirmed and best addressed in a post-approval setting, consistent with the FDA guidance document on balancing premarket and postmarket data collection. This, along with our European registry, provides a strong foundation for long-term safety.

The proposed study will evaluate serial sensor insertions and removals for 2 years in 175 patients in up to 20 clinical sites. The primary safety endpoint is the device-related or procedure-related serious adverse events through 12 months, less than or equal to 7%. The study will also assess effectiveness by comparing time in range at Month 12 and Month 1.

The post-approval study will also include additional outcome measures such as related adverse events through 2 years, any device complication, plasma dexamethasone levels at regular intervals, and the effectiveness of our training program. We will also include patient-specific outcome measures, including annual Diabetes Distress and CGM Satisfaction assessments.

As we noted earlier, we have made two design changes in response to clinical observations. These changes are relatively minor in nature and are intended to improve the function and utility of the Eversense CGM system as well as the consistency of the insertion procedure.

We redesigned the end cap to be flush with the end of the sensor, as shown on the right. Design verification testing was performed for the robustness of the new design and maintains the functional compatibility with the insertion tool. This included compressive forces and torque which may occur during a typical removal procedure.

The design of the blunt dissector tool used during the sensor insertion has also been updated to add two guide arms, indicated by the orange arrows. The blunt dissector in both versions is used in exactly the same way to create the pocket. The additional guide arms prevent any potential variability in sensor placement, ensuring proper angle of entry, depth and length of sensor placement, and that the pocket is created parallel to the skin, eliminating the risk of an angled placement of the sensor. This improvement is designed to assist in placement, which will then facilitate removal.

To validate this design change, we conducted a human factors usability study with 16 clinicians who treat patients with diabetes. Participants underwent standard safety training of the procedure, which I will describe next, and all were able to use the modified tool successfully to create a sensor pocket.

Now I will review our plans for training clinicians. One of the best parts of my job is

introducing this technology to endocrinologists and diabetologists and seeing them become comfortable and confident after only one or two procedures. Depending upon their practice, it may have been many years since they have done procedures.

The training is mandatory, comprehensive, and will replicate what is successfully done in the clinical trials and in Europe. This includes a certification process where the clinician receives instructions from Senseonics-trained observers, they watch a video, and practice the procedure with simulated skin. The initial insertions and removals are also observed by the trainer.

Before being certified, each clinician must complete the elements of the certification checklist, shown here, to the satisfaction of the trainer. The detailed checklist covers pre-work, such as videos, readings, and gathering supplies, that must be completed before the simulation, as well as the individual skills and steps directly related to insertion and removal. The checklist is not complete until the physician has undergone removal training and demonstrated proficiency.

The learning curve is often very quick, requiring approximately two to three procedures. The trainer will encourage the clinicians to schedule three patients in the same day so that they become familiar with the procedure and establish a routine.

During the training, all clinicians practice insertion and removal of the sensor using an artificial skin in a prosthetic training arm to ensure proper technique and to reinforce appropriate anatomic placement. A refresher on the principles of sterile technique, including the creation of a sterile field, is also a key part of the training.

Here are some examples of the training materials to be provided during the inpatient training. This poster details the procedure steps and can be hung in a clinic to be readily available. We are also creating a number of training videos for the various parts of the procedure, including insertion, removal, and sterile technique. There's an additional

training document to assist the clinician with potentially challenging removals. Importantly, all of these training tools are available on the website. The ability to watch approved procedure videos online also provides a convenient way for clinicians to refresh their training.

Data from June 2016 through February 2nd, 2018, indicate that 461 clinicians in 14 different countries have been trained on insertions. Ninety-four percent of those were certified by the trainer to perform insertions independently after one in-person training session. Similarly, 258 clinicians have been trained on removals, of which 86% were certified to perform removals independently after one in-person training session.

We are confident, based upon the results of our clinical studies as well as the commercial experience in Europe, that clinicians such as endocrinologists and diabetologists with minimal procedure experience can be quickly taught how to insert and remove the Eversense sensor. Our U.S. studies also support this, with 100% of the sensor insertions and 99% of the sensor removals successful on the first attempt; 91% of insertions and 80% of removals were completed in less than 5 minutes. The mean time to insert a sensor was 2.3 minutes and 4.5 minutes to remove.

Based upon the clinical data, the Eversense system has an acceptable safety profile that is appropriate for a device of this type.

There were no unanticipated adverse events during the clinical study. The incidence of device- or procedure-related adverse events was limited, and all adverse events reported during the study also resolved fully, and infections were infrequent.

Finally, there was no evidence of systemic dexamethasone exposure with single sensor placement.

There was one SAE related to the removal procedure that resolved fully, and there were no device-related SAEs.

Taken together, these studies support the conclusion that the Eversense CGM is safe for its intended use as a continuous glucose monitoring system.

Thank you. And next I'll invite Dr. Russell to provide his clinical perspective and to conclude our presentation.

DR. RUSSELL: Thank you, Dr. Kelley.

My name is Steven Russell, and I'm an Associate Professor of Medicine at Harvard Medical School, and I am a diabetologist practicing at the Mass General Hospital Diabetes Center, primarily treating patients with Type 1 diabetes, many of whom use the currently available CGM technologies. I have firsthand experience with all of the currently approved and available CGM systems dating back to 2004, and I've also published studies comparing the accuracy of different CGM systems.

I believe that CGM is the most useful and important diabetes technology that we have available today, and I encourage all of my patients to use it either in combination with insulin pump therapy or multiple daily injections.

Importantly, CGM also has tremendous potential as a critical component of artificial pancreas systems. I'm part of a team developing an artificial pancreas device that we call the bionic pancreas, and that greatly depends on CGM accuracy and reliability for proper functioning, and that has motivated my longstanding interest in new CGM technologies.

As part of the development of the bionic pancreas, I have served as an investigator in many clinical trials, and in a recent trial, we ran our own independent test of the Eversense system as an adjunctive study. In that context, I inserted and removed more than 2,000 sensors, and although I had not used a scalpel since my internal medicine residency 15 years ago, I found the insertion and removal process to be very easy, and I quickly became comfortable with it. And, frankly, it was fun to do procedures again, something I had missed.

As a diabetologist, it's frustrating to acknowledge how many of our patients are still not meeting their glycemic goals. Data from the T1D Exchange registry, as was mentioned earlier, shows that roughly 70% of patients are not at established A1c targets, and despite that, hypoglycemia is still very common. And data from randomized controlled trials has shown that CGM technology can reduce A1c and decrease hypoglycemia, both in combination with insulin pump therapy, and more recently, it's been shown in combination with multiple daily injection therapies and therefore can help to address this problem we have of poor glucose control.

And, subjectively, patients tell me that they feel much more comfortable having continuous glucose monitoring data. It gives them more control over their diabetes and confidence about their safety, and once they've used CGM, most of them never want to be without it.

Despite this, most patients with Type 1 diabetes are still not using CGM, much to my frustration, and use in Type 2 diabetes is even lower. As you heard earlier from Dr. Pettus, some of the barriers cited by patients are perceived burden of frequent repeated insertions and the fear of pain or discomfort. And one out of three patients who are using CGM at some point discontinue within the first year. Many report their CGM is uncomfortable to use or that they have problems with the insertion or retention of the sensor, and these include pain with frequent insertion, trouble keeping the sensor on during the entire wear period, or adhesive reactions.

The Eversense system addresses some of the barriers to CGM use. It has a longer sensor life so that sensors are replaced less frequently. Eversense lasts for 90 days in contrast to currently approved sensors that must be replaced weekly or every other week, resulting in 25 to 50 sensor insertions and removals each year that must be done by the patient, not by a healthcare professional.

When current sensors are in place, they cross the skin and reside in an active wound. Much less frequent insertions and the fact that Eversense resides in a protected pocket, fully healed in place, may reduce some of the discomfort associated with sensor insertion and wear.

The Eversense transmitter is particularly easy to wear. Unlike other systems, it can also be removed whenever desired without having to replace the sensor. If the transmitter falls off, glucose data is available as soon as it's replaced. As a result, the adhesive doesn't need to be as aggressive and therefore may provoke less reactions. And, in fact, a sleeve could actually be used to hold the transmitter in place, eliminating the need for adhesive entirely, and that's not possible with currently available systems.

The Eversense transmitter also provides on-body vibration alerts even when the smartphone is not nearby, such as when playing sports or when the phone has simply been misplaced. And, of course, none of us do that. Vibrations on the skin could also be used to make patients aware of alarms in environments where the auditory alerts may be missed, such as when they're sleeping or in a noisy environment. And this is a capability that's unique to the Eversense, and I think this extra measure of safety really brings a lot of value. So these unique features may address some of the barriers to CGM use and potentially expand utilization of CGM.

Based on the discussions with subjects in our study and my own patients, my expectation is that the availability of Eversense would encourage more patients with diabetes to adopt the use of CGM and enjoy both the long-term benefits of improved glycemic control and the short-term benefits of reduced hypoglycemia risks. And based on my conversations with them describing the system, I have patients who are waiting for this technology, including patients that have chosen not to use currently available CGM systems.

As an investigator, I've independently tested many CGM systems, and I have to say

I'm very impressed with the reliability and accuracy of the Eversense system. The data presented by the Sponsor today demonstrate that the device is accurate and safe, and my own experience with it gives me the highest confidence in the system.

As a physician who sees many patients with diabetes daily, I'm excited about offering this to my patients. I think that the benefits of the Eversense CGM system are numerous and certainly outweigh its risks.

So thank you for your time and attention, and Dr. Goodnow is going to return to the lectern to take questions.

DR. BREMER: Wonderful. I want to thank the Sponsor and all the Sponsor's representatives, not just for the engaging presentation this morning but also for the information that you provided the Panel beforehand for our review prior to this meeting.

So now we have -- we are ahead of schedule, so I appreciate it. So I also now will open up the floor to the Panel for any types of clarifying questions or probing questions or questions that can help elucidate the discussion. I would ask, for the matter of the minutes, if you could state your name before asking a question. And I would like to introduce one Panel member who is now with us.

Anna McCollister, would you mind giving us a quick bio or just a quick introduction now that you're here? Thank you.

MS. McCOLLISTER-SLIPP: Hi. Anna McCollister-Slipp. I'm here as a Type 1 diabetes Patient Representative. I've had Type 1 for 31 years, have all the complications, used CGM, etc. And I have no conflicts that I'm aware of.

DR. BREMER: Great, thank you.

Are there any questions from the Panel?

DR. GRUNBERGER: Yeah. This is George Grunberger. A quick question: Were there any skin characteristics which influenced the accuracy?

DR. GOODNOW: At this point we have not seen any impact. We have a relatively small population in our clinical study of African Americans, Asian Americans, and we have not seen any impact in regards to the performance either from the stability or an accuracy perspective. We do have some of the feasibility trial records, which was specifically done at a South African site where we had a much larger population. The light that is generated, of course, is completely beneath the skin; we do not read through the skin. So since the environment is all the same beneath the skin, we haven't seen any impact at all.

DR. GRUNBERGER: Thank you.

DR. TUNG: Can you describe more of the mechanism of failure? PRECISE II describes a loss of sensitivity to glucose.

DR. GOODNOW: Sure.

DR. TUNG: How does that thing know that it has lost sensitivity to glucose? I guess it's the oxidation of the fluorescent molecule, and that may be worse with reactive oxygen species. Are there predictors of failure? How does that thing know it fails?

DR. GOODNOW: So a very good question. If I could -- the single failure mode, what defines the product as being 90 days long today and what we are working on to extend it is that exact mechanism. So it isn't oxidation of our molecule that binds the glucose. There are two boron groups that bind to and grab a hold of the glucose, and unfortunately, in the environment of the white blood cells, the natural biological response to a foreign material is they will work in the area, and unfortunately, they dump reactive oxygen species, and that reactive oxygen species is what oxidizes those boronate groups to a hydroxyl group so they're not there and available to bind the glucose anymore. And it is that mechanism that we are actively working on and continue to work on. The primary reason for the dexamethasone is solely to moderate the cellular recruitment to the area so there is less insult. So it's that mechanism. As you can imagine, like you would expect with a

pacemaker, the electronics are stable for significantly longer. It's the chemistry that we continue to work on, and that is the mechanism.

DR. TUNG: So the machine knows when the sensitive glucose goes down so that when you calibrate, the gap widens? Is that how it knows it's failing?

DR. GOODNOW: Yes. However, if I could have the ADC count chart, please, to show a representative response of our device? What's on this slide -- I apologize for the detail, but this is the most core basic signal in the sensor. So it's a two-channel sensor. The red line is our reference, and that is continually monitored, and when we indicated that some of our sensors did not go to a full 90 days, the system is constantly monitoring that reference channel, and if there's a change for any reason, it would create noise or error, we actually terminate the sensor, and that's what happened in those nine cases.

What you see in the blue tracing is the ups and downs of a person with diabetes, so that's their glucose level that's going up and down over time. And I'm sure what you can visually see over the 90-day duration is that modulation or some attenuation of the signal going up and down.

So that's exactly what we monitor, and when that signal response drops to the point that we cannot maintain that mid-80s MARD, we actually turn the sensor off. So we would prefer to give no result than to give a wrong result. So it does failsafe, and that is what we actually monitor, and it is that oxidative deboronation which causes that attenuation of signal over time.

DR. BREMER: Dr. Kraft.

DR. KRAFT: What guidance would you provide to patients and caregivers for exposure to minocycline or doxycycline, tetracycline analogues?

DR. GOODNOW: Yeah. As we've pointed out, any of the tetracycline analogues, we would recommend that you not use a continuous device. They are UV-absorbing

compounds, and unfortunately, their spectral characteristics are in the area that we read, so doxycycline and tetracycline would be indicated, and we would have to train to make sure people were aware of the potential low blood sugar results you could get on the tetracycline as a family.

DR. BREMER: Dr. Gregg.

DR. GREGG: Yes, I had a couple questions about the detection of hypoglycemic excursion. I was wondering whether you could just clarify exactly how you defined hypoglycemia in that case and whether there was a subset of symptomatic cases and, similarly, whether the absolute relative difference varied across the distribution of glucose or whether it's homogeneous.

DR. GOODNOW: Sure. Could we first start with the detection response in hypo and show our sensitivity algorithm? So as we defined hypoglycemia, it's actually done analytically for this exercise. What we typically used for this exercise is 70 mg/dL for hypoglycemia as is determined by the YSI. Remember, the procedure that we use is there in clinic every 15 minutes a YSI value is obtained, and we'll compare the test device to that at the exact moment in time. So, at 70, 80, 90 mg/dL, we can actually do a characterization of what our detection rate would've been. So sorry, we'll put that up here in a second. However, the table is 70, 80, 90.

Here we go. So specifically in this case, again, it is done analytically. We can characterize hypoglycemia purely as defined by the reference glucose values. So we represent it at 70. You could set your alarm there. You could set it at 80, and of course, your detection specifics would change based on that. A representative tracing in this particular case, so this is a typical setting when a participant goes through a hypo and hyperglycemic challenge. What's shown in the blue dots, of course, is the continuous device. With the green dots is the 15 or 5 minutes during hypoglycemia response of the

laboratory analyzer.

Next, if I could show you one where we actually got it wrong, so this is a participant where you see there is a little bit of rebound glycemia just past 35.8 days where the test device, at that point, demonstrated or indicated a euglycemic value slightly above the cutoff of 70, whereas the true value was below. So that would be a missed alert. And, again, all of those are calculated analytically based on a predefined cutoff limit.

DR. BREMER: Dr. Grunberger.

DR. GRUNBERGER: Yeah, George Grunberger.

A comment and a question: Obviously, you made some design changes in the algorithm and the sensor and the insertion tools, so that's good news. This says you're learning and continuous improvement. At the same time, there's less and less data available for --

DR. GOODNOW: Right.

DR. GRUNBERGER: You're dealing with what you're proposing to be marketed. So, first, what triggered the signal to make these changes, and what's the plan for any possible changes once it's approved?

DR. GOODNOW: So I'm going to ask Dr. Jain to speak to those. Each one of them had a little bit different transmitter, for example, with certainly patient feedback and requests for smaller on-body. But we do very much view this as a continuous improvement program. This is our first generation product and since we've -- it's been 2 years, frankly, since we did this clinical study; we've been able to learn quite a bit from Europe, and that's the information we brought in. But I'd like to ask Dr. Jain to step through all of those changes very briefly.

DR. JAIN: So, specifically, as we talked about it earlier, we had four changes. The transmitter -- so I'll go through each of them and talk about what triggered the changes, the

question was. In general, it was all continuous improvement, listening to the user, whether it was commercial setting or the clinical setting. So we were continuously listening over the 2 years. We have been in the market since June of 2016 in Europe.

For the transmitter, when we do go out with the transmitter in Europe, it was the first gen device, and that's the device that we had used in the PRECISE II trial. At the same time of commercialization, we were working on the Gen-2 device, which as everybody understands would be the smaller the on-body component, the better it is for the patient from all perspectives. And it was also water resistant. The earlier one was much more prone to water damage than the new devices. So that was the motivation. It met all the requirements with the comprehensive testing very similar to what we had done for the original design.

Next, the algorithm change: Algorithm change is one thing that we have been continuously working on even from when we ran the European trial, then to the U.S. trial. From PRECISE trial to PRECISE II trial, we made some adjustments at the time, and since then, as we were refining our algorithm based on the PRECISE data, we had some changes, but we did not have the right time to bring them in. It also needed the new transmitter to bring it in because the old transmitter had memory limitations to bring in a new coordinate. So that was the reason we couldn't do it earlier and we had to come back and use the raw data that is collected in the study.

Now, as you heard me say earlier, the raw data is independent of what's going on in the transmitter, right? So it's as simple as get the raw data every 5 minutes, and then you run it through the transmitter, or in that case, we took it and ran it still through our target testing, is what we describe it, but it's through the transmitter again.

Then the third, this talks about the changes -- I think, in the interest of time, I'll skip them. The third change we made was the two other changes to the blunt dissector and to

the end cap. Those were driven from the observations that we had at the time from the PRECISE II study.

In the first one, our understanding is that as the physician, during the removal process, was grabbing on to the end of the sensor, which is where the cap is shown in blue, that's where they were exerting too much force, compressive forces, and breaking it down, and that's where the cap came off. So we made some changes to put more emphasis on reducing the variability in the manufacturing process so the adhesion is good, but then we also started out the process of designing it out completely by putting a flush end cap that the hemostat cannot grab onto anymore and so that is eliminated.

Again, the same thing, we did all the testing, whatever the requirements were for the original sensor. More importantly, the sensor dimensions, all the materials were unchanged.

And the last one was the design change in the insertion tool, which was again to take off the variability, to move the variability in the placement of the sensor with the addition of the guide marks. And, again, here we have made the change, we have done comprehensive human factors validation of the change. We have used it in feasibility studies since we do not have regulatory approval to use it in commercial settings yet in Europe, but we have used it in two of our feasibility sites, one where we have done about 28 insertions with it, another place where the other physician has done 3. In addition, we have also gone through the eight U.S. sites and the PIs, and they have all looked at the design, worked with the artificial skin, and they have all felt it will be an improvement.

DR. LIAS: This is Courtney Lias. I just want to note that we don't have the data on the sensor insertion tool from any of the studies that he mentioned.

DR. JAIN: Correct, those are feasibility sites, and we have not provided that data to FDA.

DR. GRUNBERGER: Okay, so this is a follow-up, then. If it gets approved, and since you're doing the post-approval surveys, what mechanism will you use to make any further changes?

DR. JAIN: And if it gets approved, very similar to what we're doing in European registry, we will continue to monitor, and through our vigilance program, we'll see if we see a reduction in the failure to remove sensor at the first attempt, and that's where we'll know very well how this is working. In addition, we have submitted it to the notified bodies for Europe, so we are hoping to get that run through and start getting some experience in Europe.

DR. GRUNBERGER: Okay, thank you.

DR. BREMER: Great. And before Dr. Wyne, I would like to remind the Sponsor, just because this is being recorded and will be accessible, that any unpublished data or any data that has not been presented to the FDA, we would like to recognize that just for the audience and for the record. Thank you so much.

DR. JAIN: Certainly.

DR. BREMER: Dr. Wyne.

DR. WYNE: In reading the documents, I saw that there's a recommendation that insulin injections be at least 4 inches away, and I assume that's due to the preservatives in the insulin and that would interfere with the sensor. Do you have any data, after sensor removal, of how long until that actual area could safely and accurately be used for an infusion set or injection?

DR. GOODNOW: Actually, the suggestion to keep away from the infusion site is not for any particular preservative. It actually would be to any particular transient local insulin change in the particular area as the result of the large injection of insulin in the area. So it's purely a precautionary perspective. Recall that the sensors are placed in the back of the

arm, a pretty atypical place to do an injection. Anyway, it's actually the back of the arm up here. I actually wear the device.

DR. WYNE: Your picture shows the front of the arm, it shows here.

DR. GOODNOW: I apologize, that's an error. It should be -- yeah.

DR. WYNE: So what about the question of how long until the area could be used to safely absorb the insulin after you're removed the device, the sensor?

DR. GOODNOW: As soon as the sensor is removed, it would be. Again, it's the insulin impact on the sensor itself in that local area. So if the sensor's not there, there's no impact.

DR. WYNE: So there's no inflammation and skin changes that would affect insulin absorption after removal in the area?

DR. GOODNOW: We're not aware of any changes that would do that. We have not seen any.

DR. WYNE: Have you looked at that?

DR. GOODNOW: We haven't specifically looked at insulin infusion in the area post-removal and, again, predominantly driven to the location of the sensor placement.

DR. WYNE: Okay, I'm just concerned because slender Type 1's don't have a lot of space where we can inject insulin, and I'm worried that they wouldn't be able to use that region for some period of time after removal, so that's why I was asking.

DR. GOODNOW: Okay, understood. Thank you.

DR. BREMER: Dr. Burr.

DR. BURR: A few questions. Do you anticipate that -- is it alternate arms that people use, so they do the right then the left, then the right then the left?

DR. GOODNOW: We do suggest, and in our commercial experience in Europe, it is a rotation schedule. So one cycle in the left arm and then move to the right arm. We've

recently transitioned in Europe to the 180-day version of the sensor, so it's a little bit longer time period between the two, but we do suggest the site rotation, left, right, left, right, through the training and education that we provide.

DR. BURR: Right. Do you anticipate other locations, the abdomen?

DR. GOODNOW: We would anticipate that in the future. At this point, as a first generation, we've exclusively looked at the back of the arm. It is the preferred site, although obviously not exclusive. The general preferred site for the sensor is to keep it away from the abdomen for those that are injecting or using infusion sets.

DR. BURR: Okay. Are the high and the low alarm vibrations different?

DR. GOODNOW: They are. They are the maximum vibratory energy that we can provide, so they are the most noticeable, and they are also distinct from the two.

DR. BURR: Okay. Can you reset the thresholds of alarming --

DR. GOODNOW: Yes.

DR. BURR: -- from 80 to 70?

DR. GOODNOW: Yes, the thresholds can be changed based on the patient preference as well as the provider experience as well.

DR. BURR: All right.

DR. GOODNOW: There is a low glucose alert at 60 that we don't allow you to turn off.

DR. BURR: Okay.

DR. GOODNOW: Other than that, they are variable and changeable.

DR. BURR: Rate of change is also available?

DR. GOODNOW: Rate of change as well, yes.

DR. BURR: Okay. Are there skin temperature effects?

DR. GOODNOW: There are certainly temperature effects. This is fluorescent, so the

quantum yield of that fluorescent process is quite dependent on temperature. We monitor that and measure that in two primary ways. One, there is a very specific temperature monitor inside the arm, so what we call core body temperature. There's also a thermistor monitoring system in the transmitter as well.

As I noted, the reliability of the system is about 96%. About 3.5% of that data that's not available is typically user initiated, and if they're out of compliance with our calibration scheme, the device will turn off and notify them that they don't have the potential for good validating. About a half of a percent of the time, so one to two readings per day, it's turned off for reasons such as that. For example, if you're outside and it's cold and you don't have a jacket on, you can actually drop the temperature of the local region enough that we would be concerned about the complete accuracy of the sensor. So we give you an alert that you're out of temperature range and the patients are trained to cover up, put on a jacket and the like. So it happens at a low frequency, but temperature is important.

DR. BURR: Well, what about high temperature?

DR. GOODNOW: High temperature as well, the same thing. Could I have the specifications for the system? We do actually go from 26 to 40 degrees. And recall, this is 26 to 40 degrees of the arm.

DR. BURR: Um-hum.

DR. GOODNOW: We haven't had instances of high temperature alarms. We will, as I said, rarely do get low temperature alarms, but it's pretty hard to get the arm above 40 degrees even with a fever.

DR. BURR: You can do it in a marathon in hot weather.

DR. GOODNOW: That, we do. And we actually have a fair number of European users that appreciate the attributes of the adhesive material for sweating, so we certainly do see that. But the 40-degree upper limit has not been an issue.

DR. BURR: Okay. Is it recharged once a day for 3 minutes? That's kind of --

DR. GOODNOW: The use process that we recommend is actually, you take the entire system off when you shower; you actually get to clean the area, replace the adhesive. The transmitter is designed with a very rapid charge battery, so it is put into a cradle and recharged. It has a useful life of at least a year, which is really defined by that ability to recharge. But at that time period, you are without glucose results during that because you do have the system off. But as you may note when I referenced the 23.4 hours a day is a very common use, and that's actually the 20 minutes of people shower cycle.

DR. BURR: Okay, all right.

DR. GOODNOW: And they are recharging.

DR. BURR: How water resistant is it?

DR. GOODNOW: It's IP67, so you cannot scuba dive with it, but you can be submersed for a half an hour in a meter.

DR. BURR: All right, so swimming.

DR. GOODNOW: Swimming is acceptable, showering is acceptable, hot tub is acceptable, but scuba diving we would not like you to do, and we will train against that.

DR. BURR: How many days or hours after the actual insertion procedure can the transmitter be applied to the skin over the sensor?

DR. GOODNOW: You can put the transmitter over immediately, but for 24 hours after the insertion it is in a quiet initiation process. So it's a 24-hour startup period with this insertion.

DR. BURR: Okay. Is it possible to overlap them so people don't have --

DR. GOODNOW: Sure.

DR. BURR: Or blank time?

DR. GOODNOW: Sure. And we've had people do left-right in that, correct.

DR. BURR: Okay, all right. Thanks.

DR. BREMER: Dr. Gregg and then Dr. Wyne.

DR. GREGG: I was wondering, is there an effect of dehydration or hydration on the accuracy? And, secondly, to the extent that temperature does affect the accuracy, do you know which direction it moves, or is it just poor?

DR. GOODNOW: We haven't extensively studied dehydration with enough to draw a definitive conclusion. From a temperature perspective, it is a known response; it's actually the quantum yield of the fluorescence process. So that is incorporated into our glucose algorithm, so we do modify the amount of light translated into glucose based on temperature, and we very specifically use that.

DR. BREMER: We're going to go to Dr. Wyne and then Dr. Goldsmith and Dr. Lakos and then Anna will have the last questions. I guess we'll round out because I want to make sure that we finish by 10:00 and have time for the Sponsor to reply.

DR. GOODNOW: Thank you.

DR. WYNE: So I have two fairly quick questions, and one is just coming from my patients. Related to the temperature question, have you done any studies with respect to submersion in hot tubs? Because my patients ask me that.

DR. GOODNOW: Unfortunately, we haven't done any controlled studies. We do have reports of it, but I don't have any controlled studies that would be appropriate or --

DR. WYNE: Do you know what the anecdotal reports were?

DR. GOODNOW: The anecdotal is people do indicate -- again, it's also on our arm, right? We're not aware of any off-label use on an abdomen, so it's actually pretty high up, but that's pretty acceptable.

DR. WYNE: Okay. In terms of the alerts, and he was asking you about what you could set the alerts at, as I read through -- I think it took a while, but I sorted out the

difference between the actual target setting and the alert setting, but my understanding is the alert settings are always on, so you cannot turn off a high or a low. You have to have a high or a high or a low on at all times.

DR. GOODNOW: The alarm you can't turn off is the low.

DR. WYNE: You can turn off the high?

DR. GOODNOW: Correct.

DR. WYNE: Okay.

DR. GOODNOW: Is that correct?

(Off microphone response.)

DR. GOODNOW: I'm sorry, 350 limit. I'm sorry, 350 limit that you cannot turn off.

DR. WYNE: Okay.

DR. GOODNOW: You can go lower, and a 60 limit.

DR. WYNE: But low can be set as low as 60 but as high as 115?

DR. GOODNOW: Correct.

DR. WYNE: But you can move that around; the 60 is not an absolute invariable. So if they wanted to set it at 100, they could --

DR. GOODNOW: Yes.

DR. WYNE: -- and it would not be at 60.

DR. GOODNOW: Yes.

DR. WYNE: But high cannot be turned off?

DR. GOODNOW: Yeah, on 350, correct.

DR. WYNE: Okay, thank you.

DR. BREMER: Dr. Goldsmith.

DR. GOLDSMITH: This is Barbara Goldsmith.

Two quick questions: Just for clarity, you are seeking approval for both patients with

diabetes Type 1 and 2, because the slides didn't really distinguish?

DR. GOODNOW: We do; we are seeking approval for people with diabetes, so that would include Type 1 and Type 2. From our clinical testing, the majority of the testing is done in people with Type 1 diabetes; that is the largest use in the commercial setting, but it's also a much greater glycemic excursion, so we can test the sensor much more rigorously. But about 25 to 30% of our participants were Type 2's, the majority of which were on insulin.

DR. GOLDSMITH: Okay. And my second question has to do with the home blood glucose meters that you compare to. Was there one type of meter selected, or did you have multiple? And if so, was there variability seen with the correlations?

DR. GOODNOW: We tested it or we used it in the clinical setting at two different commercially available, United States commercially available meters. We did not see a difference between the two meters, but frankly, we didn't systematically look at it. The primary reference is the hospital analyzer, the YSI, the Yellow Springs Instrument analyzer. But we didn't see it in the home setting, a difference to commercial blood glucose meters, right.

DR. GOLDSMITH: Thanks.

DR. GOODNOW: The performance of those devices has gotten significantly better over the years, at least those two devices, and they perform quite well.

DR. BREMER: Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

So you presented data, accuracy data up to 90 days, and you also stated that if the sensor stops working, the functionality is lost. But, obviously, you have also shown that, at 90 days, majority of your devices still functional. So what's happening after 90 days? Let's say the patient doesn't or is not able to return for removal.

DR. GOODNOW: It is a good question. An important part of our training and introduction, we actually encourage the users to set an appointment for the actual removal and replacement, if they choose to do that at the 90-day time period. There are 7 grace days, so it will actually function through Day 97, but then the device is turned off, as we don't have data in the United States to confirm any performance beyond that. There is a timer, a warning system, if you will, that starts at 30 days, and it counts down and will tell you every day with a specific acknowledgement at 30, 14, and 7 days that you're coming up on your 90-day, and then you still do every small 7-day window after that.

DR. BREMER: Ms. Petersen.

MS. PETERSEN: Thank you. Carolyn Petersen.

I have four questions. First, can the transmissions be detected by nearby devices outside the wearer?

DR. GOODNOW: The wireless transmissions?

MS. PETERSEN: Um-hum.

DR. GOODNOW: There are two wireless technologies that we use; both are standard and off the shelf, if you will. The wireless to the sensor is near field; it's the same technology that you use for key card access to your building. That has a range of about 2 cm. It is specifically paired and secure, so even if you could get within 2 cm, you can't interpret it, but even the 2 cm is pretty restricted by the zone. The other technology is the commercial low-energy Bluetooth, which is how we go to the smartphones. So that is visible, but the Bluetooth technology is encrypted and generally protected and very specific for our transmitter when you pair those together. So the Bluetooth, yes. The NFC, no.

MS. PETERSEN: And is location data, as to the wearer, transmitted within part of that transmission?

DR. GOODNOW: Location data is not. It's complete patient choice as to whether

they ever wanted to leave their phone. If they would like to store it and archive it and share it, it does need to go to the cloud, but the device is fully effective if they choose not to do that.

MS. PETERSEN: And then I take it the data can be saved by the patient, you're saying?

DR. GOODNOW: Can be saved by?

MS. PETERSEN: By the patient.

DR. GOODNOW: By the patient, yes. There's 90 days' worth of data on the transmitter, there is the complete storage history on the phone, and then if you choose to share it to the cloud, there will be that permanent storage on the cloud. But, again, that is patient selectable.

MS. PETERSEN: And then I have two questions related to the postmarketing training and survey. First, what are the plans for training family physicians and internal medicine providers, nurse practitioners and physician assistants? Because many patients don't have access to a diabetologist or an endocrinologist, as was mentioned in the presentation.

DR. GOODNOW: Okay. I'd like to have Dr. Kelley speak to our training program. It emulates what we're doing in Europe to some degree.

DR. KELLEY: Lynne Kelley.

Our training program is designed at first launch for endocrinologists and diabetologists. We are evaluating that expansion beyond, but at the current time, our label indication and our training program is designed for the endocrinologists. We recognize that patients with diabetes are treated at a very broad level of clinics and exposures, but that would be next steps in expansion indication.

MS. PETERSEN: Okay. And my last question has to do with what patient-related outcomes will be included in the postmarket study.

DR. KELLEY: So, primarily, we'd be looking at standard measures such as improving the hemoglobin A1c, improvement in the time in range, knowing we're migrating more towards a time in range function. And then also, as I mentioned, the Diabetes Distress Scale and the CGM Satisfaction Scale.

MS. PETERSEN: Thank you.

DR. BREMER: Ms. McCollister-Slipp.

MS. McCOLLISTER-SLIPP: Hi there. I have several questions. So, just so that I'm clear, so the comparator data, when you're talking about accuracy, you're saying the primary accuracy is determined by in-hospital or in-clinic data.

DR. GOODNOW: Correct.

MS. McCOLLISTER-SLIPP: But it's calibrated twice a day. So if I, as a patient, am trying to understand the accuracy --

DR. GOODNOW: Um-hum.

MS. McCOLLISTER-SLIPP: -- I'm not going to the clinic every day, so how do I understand based on your studies how accurate it is? Is it just based on those two daily calibrations?

DR. GOODNOW: It's calibrated based on the two daily calibrations. The result that you get, the accuracy of the result that you get, will be representative of the hospital analyzer comparator. Now, it's true, you don't have the ability to see that. What you actually look at is the results on your home blood glucose meter and what your continuous device might say at the same time. Because the home blood glucose meter is not as accurate, you will get a higher level of apparent error between the two because it's the total of the error in the CGM plus the total of the error in the home blood glucose meter. We are pretty confident, based on the testing we've done, that the error that's in the CGM is that 85 to 87%, 15/15 metric that we showed. It drops about 10%, which is pretty typical

when you compare it to a home blood glucose meter because that error is also built in into the reading as well.

MS. McCOLLISTER-SLIPP: But in terms of the accuracy that you've demonstrated in the studies, that is primarily based on like the day-to-day accuracy. I'm assuming you didn't have people coming to the clinic once a day because --

DR. GOODNOW: Correct.

MS. McCOLLISTER-SLIPP: -- if you're looking at excursions --

DR. GOODNOW: Right.

MS. McCOLLISTER-SLIPP: -- I mean, the CGM I currently use, you know, obviously, the 20/20 rule or whatever it is, but there's a much bigger differential on accuracy as you get into higher ranges or lower ranges. So the accuracy that you're reporting is based on what, just assuming that the data is accurate because it's accurate within the clinic?

DR. GOODNOW: Correct. That's the comparator that we all standardize to, right.

MS. McCOLLISTER-SLIPP: Okay. Let's see. So you said that you don't have that much data on hydration. Have you looked at that at all specifically, or do you have anecdotal data from the --

DR. GOODNOW: We haven't looked at it systematically enough to have any definitive conversation. We do have a fair number of marathon runners, swimmers, extreme bikers that have been attracted to the system, and we know that there's good performance there, but that is completely anecdotal.

MS. McCOLLISTER-SLIPP: Right. Are there any plans to look at that specifically?

DR. GOODNOW: That is certainly something that we consider. You know, we're here, as well as the Agency, to hear the feedback from the Panel.

MS. McCOLLISTER-SLIPP: And is there any reason, from an electrochemical perspective, in terms of the way that the system works, is there any reason to think that

hydration could impact accuracy?

DR. GOODNOW: The issue with hydration is frankly the physiology of the interstitial fluid environment that, I think, all sensors would be impacted. So I don't think there's a technical reason why this particular sensor would be impacted any more or less than any system that measures interstitial fluid. But hydration does have the ability to change that dynamic, so I think that it potentially could be there as well. I know there's been some investigations in the hospital setting in other areas for CGM, for hydration, but I think we would be subject to those same limitations because we're all in the same test fluid, that being interstitial fluid.

MS. McCOLLISTER-SLIPP: Have you done, in terms of the patient population -- and forgive me if I missed this, did you look at range of ages, in terms of pediatric through elderly or --

DR. GOODNOW: We have not evaluated pediatric at this point. It is something that we will get to. And this is an adult request. If I could have the age demographics? The other that we specifically looked at is BMI. I'll put this up, but if you could bring me the -- well, that will actually work as well. A forest plot which shows all of it, male, female, age, the breakdown, young adults to middle age to -- we did those six folks in the PRECISION study that were above 65. We do have additional data on PRECISE II. BMI range from below 25 to above 25. And then Caucasian, very small African American and Asian. This was a small 35-patient study. Shown here is the PRECISE study and those demographics. A little bit larger differentiation in race in the 90-patient but still very heavily weighted towards the U.S. test population of Caucasian.

MS. McCOLLISTER-SLIPP: And then what about people with complications, microvascular complications?

DR. GOODNOW: We didn't extensively look at complications at that level as part of

the clinical study.

MS. McCOLLISTER-SLIPP: Do you have any people -- I mean, I'm assuming, did you ask people about that as they were entering, whether or not they did have microvascular complications?

DR. GOODNOW: I don't specifically know if they asked about microvascular complications. Katherine, do you know? It was an exclusion, so no.

MS. McCOLLISTER-SLIPP: It was an exclusion criteria?

DR. GOODNOW: It was an exclusion, correct.

MS. McCOLLISTER-SLIPP: So you have no data at all on people --

DR. GOODNOW: Correct.

MS. McCOLLISTER-SLIPP: -- like me who have microvascular complications?

DR. GOODNOW: Correct. At this point, yes.

MS. McCOLLISTER-SLIPP: Have you done -- well, I guess, in the registry, have you -- in the European registry, have you seen any off-label use of the device, just in other sites, other places?

DR. GOODNOW: I actually have not heard of any off label in the European registry.

MS. McCOLLISTER-SLIPP: I know you're planning for a specific label, so --

DR. GOODNOW: Right.

MS. McCOLLISTER-SLIPP: -- I'm just curious.

DR. GOODNOW: Right. No, no. I'm not sure if --

(Off microphone comment.)

DR. GOODNOW: Okay. Sorry, yes.

DR. KELLEY: Lynne Kelley.

We have had requests for a few off label, and we discussed with the physician directly the reason why we recommend use of the arm site and that we would be

entertaining alternative sites for exploration, but right now our data suggests consistency and accuracy in the arm location.

MS. McCOLLISTER-SLIPP: Okay. Sorry if my questions are kind of lots of different other -- lots of different topics. So when you take the transmitter off, what happens to the data that could be collected during that period of time? Does the sensor retain it, and then when you reconnect to the transmitter, do you get it, or is the data lost?

DR. GOODNOW: The data is lost. This technology, what's implanted, as Dr. Jain indicated, is predominantly an antenna, so the battery in this case is on the outside. So if we take that battery away, the sensor is completely dormant during that time period. So that 20-minute shower period, you don't have continuous. It does have the advantage that as soon as you put it back on, it starts right up again and picks up where it left off. But unfortunately with this technology, as there's no power, there's no battery that's implanted, it is dormant.

MS. McCOLLISTER-SLIPP: Okay. So if I go to a gala or I'm wearing something sleeveless and don't want the transmitter attached, then essentially I'm without data and have no ability to get that data?

DR. GOODNOW: Correct. We ask the users that do that in Europe right now is they'll go back to finger sticking, and as an adjunctive device, they do typically carry that for calibration and for their confirmatory testing as well. But that's correct with this technology. The only way that we can get the sensor as small as it is, is to not implant a battery.

MS. McCOLLISTER-SLIPP: Right. And then from the charger cradle perspective, can it be charged without the cradle? So if I like travel and forget my cradle -- which I will never do that, I'm sure, but --

DR. GOODNOW: That's very good, and unfortunately, it is a custom cradle because

the prior generation, the one that we're seeking approval to change, could be generic because it is just micro-USB. Unfortunately, the micro-USB port is the water ingress port, so that's where you lose the ability to swim and shower. So the second generation that we're looking for approval to use is contact, like your toothbrush at home -- that's where waterproof comes from -- but, unfortunately, that does take a custom cradle. So we are routinely providing many of those free of charge for people to throw in their travel bag and have it work and the like, should they like to have those.

MS. McCOLLISTER-SLIPP: So I can call you and have it FedExed to --

DR. GOODNOW: That's correct, yes.

MS. McCOLLISTER-SLIPP: -- whatever hotel I happen to be at?

DR. GOODNOW: Absolutely. And you can call me.

(Laughter.)

MS. McCOLLISTER-SLIPP: Good to know.

DR. BREMER: And Anna --

MS. McCOLLISTER-SLIPP: Good to know.

DR. BREMER: Anna, we have two more questions after you, so that's the last question, please. Thank you.

MS. McCOLLISTER-SLIPP: Last question. So from the scuba diving perspective, as someone who occasionally scuba dives when it's really warm outside, does the sensor have to be removed?

DR. GOODNOW: No, no, no. No, no. No, it's just the transmitter.

MS. McCOLLISTER-SLIPP: Just the transmitter.

DR. GOODNOW: Just for water ingress in the transmitter. The sensor is -- once you're been through that 48-hour of healing --

MS. McCOLLISTER-SLIPP: Yeah.

DR. GOODNOW: -- you're water tight again, so you're completely free --

MS. McCOLLISTER-SLIPP: But it's also pressure tight, it's not going to explode with --

DR. GOODNOW: No, no, no. No, no, no, no. Nowhere near the pressure.

MS. McCOLLISTER-SLIPP: Okay, thank you. That's all.

DR. GOODNOW: You would have bigger problems with that amount of pressure that it would take to crush the sensor.

MS. McCOLLISTER-SLIPP: I'm sure I would.

DR. BREMER: Thank you. We have Dr. Tung and then Dr. Rendell, and then we'll take a break.

DR. TUNG: I am imagining a patient with this device who presents for elective surgery or for admission to the ICU and the risk of chronic long-term exposure to dex and adrenal insufficiency. Do you have any experience with that in the European trial data so far? And can you describe these two cases of hyperpigmentation in a little bit more detail to understand that?

DR. GOODNOW: Sure. Let's take the dexamethasone. These are very, very small traces of dexamethasone quantity. The total device is loaded with 1.75 mg, but frankly, it's only loaded to that level so that it can actually deliver 300 µg per sensor. So after about 100 days, that's about 3 µg per day. It is the typical water insoluble dexamethasone acetate for that dissolution, so we're actually looking to deliver a very, very small quantity. We have evaluated the appearance of any systemic level of dexamethasone, and with a single sensor, it is not at all observable in the immunoassays that we've looked at, the assays that we've looked at any point with a single sensor at 50 pg/mL. You can see very, very trace amounts of dexamethasone in those patients that had two sensors, so essentially twice the challenge concentration. But from a systemic perspective, it just never builds up to that level that you could detect it systemically.

And I think, Nick, could you come and speak to what we know about the systemic needs of dexamethasone to have a physiological effect or certainty to impact somebody with diabetes?

DR. FLEISCHER: Good morning, my name is Dr. Nicholas Fleischer. I am the Vice President of Clinical Pharmacology and Biopharmaceutics at the Weinberg Group.

So we know that pharmacology of dexamethasone is well understood, and we know that even at single doses of 50 µg, there's no systemic pharmacologic response from that. And as was just said earlier, with the assay that we used in measuring the dexamethasone levels in the subjects that had the sensor implanted, it had a precision of 50 pg/mL, a very highly sensitive assay, and we could not detect any dexamethasone in those patients. So as was just said, the pharmacology is well understood, but we do not get any levels of dexamethasone that would be pharmacologically effective. So, in response to your question about any concern with HPA axis suppression, because the levels are so, so low, even non-detectable, we do not expect that to be a problem.

DR. TUNG: Do you believe these hyperpigmentation episodes were due to dexamethasone or not?

DR. GOODNOW: It is likely that those are dexamethasone related. I'd like Dr. Kelley to speak to our experience.

DR. TUNG: Go ahead.

DR. KELLEY: We have seen some very few instances of hyperpigmentation at the level of the sensor. In the PRECISION study we had one patient, only one patient in -- reported in both arms because it was a dual patient. And so we have seen a slight discoloration. That patient did not report -- or examination at the Day 60 mark, showed nothing. At the time of the 90-day, the final presentation, they did report the slight bluish discoloration, but at removal, at the post-removal, it was completely gone. So very

transient, late in the life, believed to be related to dex, but again, following. And we've had a few dex-related or we are assuming to be dex-related in the European registry with a slight amount of discoloration, again all completely resolvable.

DR. TUNG: One last quick safety question. For the in-hospital setting, is this device MRI safe?

DR. KELLEY: Sure. Currently, there's a warning against MRI use because of the -- we are doing the testing for that, but the product label, just like other implantable devices, includes a patient warning card, a notification and instructions to patient upon insertion.

DR. BREMER: Dr. Rendell.

DR. RENDELL: What is your experience in skin-of-color patients?

DR. GOODNOW: We, unfortunately, do have a relatively small population. I think, on the demographics slide, if I could have the PRECISE stuff slide again, there were seven categorized as black/African American. Seven percent -- I'm sorry, the number is approximately seven or eight people, a couple of Asians, and a couple that did not identify. So it is a small population. As I said, in other studies, we do have some greater indication, but since there's no through-skin component, there's no optical impact to the outside of the skin color. We're all measuring in the local fatty tissue just beneath the skin.

DR. RENDELL: Do you expect any effect of skin color on transmission?

DR. GOODNOW: No. No, we do not. This is a near field transmission, very, very low energy, no indication of any impact at all.

DR. BREMER: Great, thank you. I want to thank everyone for a nice and robust discussion, the Sponsor and the Panel members.

We will now take a 15-minute break. Before you go, though, Panel members, I'm asked to say that please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience during our break. We will get back on

schedule. Please be back here by a little after 10:15, and we'll resume at 10:20 with the program. Thank you.

(Off the record at 10:06 a.m.)

(On the record at 10:23 a.m.)

DR. BREMER: So, for the minutes, it is now, according to iPhone, 10:23, and I would like to call the meeting back to order. Staying with the program, our next agenda item is the FDA presentation.

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

I now do invite the FDA to give their presentation, and they have 75 minutes to present. So, Dr. Lias, thank you, and the FDA, thank you very much.

DR. BALSAM: Just a second while I get situated up here. So good morning. Thank you for taking the time to participate in our Panel meeting. My name is Joshua Balsam, and I am a medical device reviewer in the Diabetes Devices Branch in the Division of Chemistry and Toxicology Devices.

The purpose of today's presentation is to discuss the Senseonics Eversense Continuous Glucose Monitoring System. In the first several slides of our FDA presentation, I will be giving you some background information that is relevant to this type of device. In the subsequent slides I will be presenting a summary of the studies that have been conducted by Senseonics to support premarket approval for this device. First, I will briefly review some of the basics about home glucose monitoring.

In order to maintain control of their glucose levels, many people with diabetes need to monitor their glucose levels frequently, typically several times per day. Currently, there are two options that people have for measuring their glucose levels when they're at home.

The standard of care for managing blood glucose in people with diabetes involves periodic self-monitoring of blood glucose with portable blood glucose meters. This self-monitoring is known as SMBG. The measurements require a drop of blood, which is obtained with a finger stick.

I guess I can't use the little two-finger slide thing to scroll my notes, so excuse me while I adapt.

Another option for monitoring glucose at home is a continuous glucose monitor, or CGM. CGMs provide a continuous series of glucose readings with a new glucose reading being determined every few minutes. Though for each measurement point CGMs have a lower accuracy than SMBGs, CGMs do have other features which provide additional information to the user. Real-time glucose results may be displayed along with a trend line graph for recent glucose readings. Trend information provides the direction in the current glucose trend and the approximate rate of change.

I will now be discussing the Eversense CGM system, including how the Eversense system is different from other approved CGM systems.

So the specific design of the Eversense CGM system was presented in detail by Senseonics previously. To recap, the system consists of a sensor, a transmitter, and a user interface in the form of a mobile application, or mobile app, which is installed on a smartphone or tablet.

Senseonics has proposed indications for use for the Eversense system. These indications specify that the system is for adults ages 18 years and older, the system is meant for tracking and trending glucose information, the system provides alerts for detecting and predicting high and low glucose events, and that SMBG measurements should be used for all treatment decisions.

Some CGMs have similar indications for use to these. Other CGMs have different

indications for use, such as being indicated for use in children down to age 2 or being indicated for standalone use, meaning that the CGM values can be used directly to make treatment decisions without confirmation in those other approved CGMs.

There are a number of differences in the physical design between the Eversense CGM and other approved CGMs. For example, in all previously approved CGM systems, they use a thin wire-like sensor which is inserted through the skin at home by the user. This insertion is done using a small-gauge needle. In the Eversense CGM system, the sensor is larger and is implanted under the skin during a minor surgical procedure in a physician's office. The Eversense CGM sensor would be the first fully implanted sensor for a CGM system. Also, in other CGM systems, the sensor is physically connected to the transmitter. In the Eversense system, the sensor and transmitter are connected wirelessly.

The wear time for the Eversense CGM sensor is up to 90 days. Currently approved CGMs have sensors that last between 6 and 14 days. Said another way, the Eversense CGM sensor would last between 6 and 12 times longer than other currently approved CGM sensors.

So, also, all previously approved CGMs have used very similar glucose sensing technology. They've all used variations of the glucose oxidase enzymatic reaction, and they've all measured the output of this reaction electrochemically.

The Eversense CGM sensor uses a fluorescence sensing mechanism. A fluorescent polymer coating on the outside of the sensor is excited by light from an LED inside the sensor. The glucose from the body reversibly binds to the coating, and the amount of light emitted by the polymer coating rises and falls with glucose concentration. This emitted light is measured by photodetectors inside the sensor.

If approved, the Eversense CGM sensor would be the first to contain a drug component, dexamethasone acetate, or DXA, which is a corticosteroid.

During early feasibility testing, Senseonics found that the fluorescent molecule responsible for detecting glucose was degraded by reactive oxygen species found in the body. These reactive oxygen species are part of the body's inflammation signaling pathway. To reduce their concentration, Senseonics added a dexamethasone-eluting silicone collar to the outside of the Eversense sensor in order to reduce the local inflammation. This collar contains 1.75 mg of dexamethasone acetate.

Another notable difference between the Eversense CGM system and other approved CGMs is the area in which the sensor can be inserted. The Eversense CGM is limited to being inserted in the outside -- the outer side, pardon me, of the two upper arms. This is the only region where repeat sensor insertions could take place. Other CGMs can be inserted on the abdomen, the upper buttock, and/or the back of the upper arm.

We will now discuss some of the bench testing that was conducted to evaluate the performance of the Eversense system and which Senseonics is using to support approval of their device.

Senseonics has conducted some bench testing to assess the potential sources of chemical interference for the Eversense CGM sensor. Chemical interference can occur in a CGM sensor if the sensor incorrectly responds to a molecule other than glucose. Understanding what substances can interfere with a CGM is important so that sensors can be evaluated for safe use in the expected use environment. In addition, CGM users can be informed about what substances they need to avoid while using the device.

All chemical sensors, such as CGMs, have the potential for interference. Exactly which substances will interfere with a particular CGM depends on the specific chemistry for the sensor. Because the Eversense sensor has different chemistry than other CGM sensors, it has different sources of chemical interference.

For the Senseonics sensor, under normal operation, glucose binds to available sensor

sites on the fluorescent polymer which causes the measured glucose value to go up. Other molecules that are sufficiently different from glucose cannot bind to these sites, so they do not affect the glucose measurement. Interference occurs when another molecule is able to bind to a site on the polymer.

Interference can cause the CGM glucose value either to go up or to go down. If the interfering molecule occupies a binding site but does not cause fluorescence, it is preventing glucose from binding, which artificially lowers the glucose measurement. Conversely, if the interfering molecule is similar enough to glucose that it causes fluorescence, this artificially increases the glucose measurement.

Senseonics performed in vitro bench testing to assess potential sources of chemical interference. Forty-one potentially interfering substances were tested. Testing was conducted by using the Eversense system to measure the concentration of glucose in a prepared solution both before and after the addition of a potential interferent. The initial concentrations of potential interferents were chosen based on available information in sources such as standards, guidance documents, and available published literature.

If interference was observed at the initial concentration of a particular substance, then dose-response testing was conducted to determine the concentration below which there was no interference. The lowest interferent concentration which still interfered was then compared against data available in literature to determine if such a concentration was likely to occur when patients use a CGM.

The in vitro bench testing results found that tetracycline, an antibiotic, is a source of interference at concentrations that may result from therapeutic uses of the drug. Tetracycline falsely lowers the measured glucose value; that is, it introduces a negative bias. A negative bias may have negative clinical consequences if the CGM value is used to influence treatment strategy.

Mannitol was also identified as an interferent during bench testing. Mannitol can falsely raise the measured CGM value; that is, it introduces a positive bias. The high concentration of mannitol that is required to cause interference is unlikely to result from the normal dietary intake of the substance. However, there are medical procedures that involve IV administration or that use mannitol irrigation solutions which would result in sufficiently high concentrations to cause interference.

Sorbitol and other sugar alcohols were tested as well, and they did not show interference at lower concentrations that would be likely to result from dietary intake. However, sorbitol is also used in irrigation solutions for some procedures, so Senseonics has identified it as a potential interferent in those situations.

Senseonics has proposed to include a contraindication in the Eversense labeling regarding the potential for mannitol or sorbitol to cause falsely elevated readings when administered intravenously or as a component of an irrigation solution or a peritoneal dialysis solution.

Senseonics has proposed to include a warning in the Eversense labeling to inform users that the use of tetracycline may falsely lower sensor glucose readings and that they should not rely on their CGM system while using tetracycline.

The Agency would like input from the Panel regarding whether these labeling mitigations are appropriate and adequate.

I would now like to invite Dr. Jisun Yi, who will be presenting the clinical studies that have been conducted to evaluate the performance of the Eversense system and which Senseonics is using to support the approval of their device.

DR. YI: Thank you, Dr. Balsam.

My name is Jisun Yi, and I am a medical officer for the Diabetes Devices Branch in the Division of Chemistry and Toxicology Devices.

I will now discuss the two primary clinical studies that Senseonics is using to support approval of the Eversense System. The PRECISE II study was conducted first and included 90 participants enrolled at eight U.S. sites. The PRECISION study was subsequently conducted and included 35 participants enrolled at three U.S. sites.

The PRECISE II study included 90 study participants who were initially enrolled and had Eversense sensors inserted. The study included in-clinic accuracy assessments on Days 1, 30, 60, and 90 of sensor wear.

During the PRECISE II study, performance of the Eversense CGM system was assessed during four in-clinic sessions held on Days 1, 30, 60, and 90 of sensor wear. The Day 1 in-clinic visit lasted 4½ hours. Subsequent visits then lasted 12½ hours.

Visits on Days 30, 60, and 90 included various challenges. Glycemic challenges were used to drive participants' glucose high and low in order to assess system performance across the range of glucose values. The effects of upper arm exercise were assessed by having participants who had sensors inserted in both arms exercise one of their arms for 30 minutes. The effects of sensor site compression were assessed by having participants with two sensors inserted lie on their side for 30 minutes to apply pressure to the sensor site. During these challenges, frequent blood glucose measurements were obtained to assess system accuracy.

Between the in-clinic visits on Days 1, 30, 60, and 90, participants were sent home with the Eversense CGM system. The system output was blinded so participants could not see CGM values or receive glucose alerts during at-home use. Participants continued to receive calibration alerts and were required to enter SMBG calibration values twice per day. Participants were requested to collect four to seven SMBG measurements total per day.

Of the 90 study participants who started the study, 40% were female, 60% were male. Mean age was 45 years with a range of 88 -- sorry, 18 to 77 years. Mean body mass

index was 29, with a range of 19 to 50. Sixty-eight percent of study participants had Type 1 diabetes; 32% had Type 2. Seventy-eight percent of study participants were on insulin therapy.

One representation of Eversense CGM system accuracy, as measured during the PRECISE II study, is presented here. There are a number of ways to represent accuracy of a CGM system. This table presents the rate at which CGM system values agreed with paired measurements made by a laboratory comparator method to within 15 mg/dL or 15%, depending on whether the blood glucose measurement was below or above 80 mg/dL. For each in-clinic accuracy visit day, the results are broken down by glucose range.

Because the in-clinic visit on Day 1 only lasted 4½ hours, there is less data available on that day. Also, Day 1 did not include glycemic challenges, so there was little data available in the hypoglycemic range. For example, in the range of 40 to 60 mg/dL, there were 20 data points for Day 1 compared to 180 data points on Day 30. From this data, system accuracy on Day 1 appears to be worse than on subsequent days, particularly in the hypoglycemic range. However, given the long period of time between in-clinic sessions, it is not clear how system accuracy may change between Days 1 to 30.

SMBG data was available between Days 1 to 30 of the sensor wear period in the PRECISE II study. High-level data from SMBG measurements from the PRECISE II study broadly indicate that performance may improve gradually between Days 1 and 30.

It is important to understand what system accuracy looked like during the early wear period, when the wound healing process associated with sensor insertion would occur, in order to accurately assess the safety and effectiveness of the system.

SMBG is less accurate than the comparator method used during in-clinic visits, so this SMBG data should not be considered as representative of the Eversense system accuracy. Rather, it is intended to provide a general idea about trends in system

performance over time.

Senseonics provided an overview of all PRECISE II study adverse events in their presentation. Here we will discuss the adverse events related to sensor removal.

During the PRECISE II study, there were three adverse events related to removal of the sensor, one of which was categorized as a serious adverse event. In the serious adverse event, two unsuccessful attempts were made to remove an Eversense sensor from a participant's arm. In the second attempt, ultrasound was used to try to locate the sensor. For the third attempt, which was successful, a general surgeon was used to perform the removal. The patient was put under general anesthesia, and fluoroscopy was used to locate the sensor.

Two adverse events occurred in which sensor end caps were noted to be missing after sensor removal. Because the end caps could not be located, a worst-case assumption is that the end caps were left in the patients' arms. In both cases, investigators concluded that the risks posed by an exploratory surgery to locate and remove the end caps were greater than the risks posed by leaving the end caps in place under the skin.

Following the PRECISE II study, Senseonics conducted a subsequent clinical study, referred to as the PRECISION study. This study included 35 participants. The PRECISION study was similar to the PRECISE II study in that it included in-clinic accuracy visits, with participants using the device at home between visits. In the PRECISION study, the Eversense device was not blinded during at-home use, so participants could see CGM values and receive glucose alerts.

To address the question of how system performance changed between Days 1 to 30, the PRECISION study included two additional in-clinic accuracy assessments on Days 7 and 14. Also, glycemic challenges were added on Day 1 of the study in order to ensure that sufficient accuracy data was collected across the measurement range of the Eversense

system.

In-clinic sessions lasted between 14 and 19 hours, including two overnight sessions on Days 7 and 14 to assess system accuracy while participants slept. Accuracy assessments were conducted similarly to the PRECISE II study, including frequent blood glucose measurements with a laboratory comparator method and glycemic challenges to ensure that measurements were collected across the glucose range. All study visits included blood tests to assess systemic exposure to dexamethasone.

Of the 35 study participants in the PRECISION study, 49% were female, 51% were male. Mean age was 51.6 years with a range of 18 to 75. Mean body mass index was 28 with a range of 19 to 44. Seventy-one percent of study participants had Type 1 diabetes; 29% had Type 2. Eighty-six percent of study participants were on insulin therapy.

One representation of Eversense CGM system accuracy, as measured during the PRECISION study, is presented here. This table presents the rate at which CGM values agreed with paired measurements made by a laboratory comparator method, to within 15 mg/dL or 15%, depending on whether the blood glucose measurement was below or above 80 mg/dL. For each in-clinic accuracy visit day, the results are broken down by glucose range. Similar to the PRECISE II study results, system accuracy on Days 1 to *7* appears to be worse than on subsequent days, particularly in the hypoglycemic range.

Senseonics provided an overview of all PRECISION study related adverse effects in their presentation. Here we will discuss the adverse effects related to sensor insertion and removal.

During the PRECISION study, there were three instances in which investigators had difficulty removing Eversense sensors. Two of these cases were labeled as adverse events; one was labeled as a protocol deviation.

The two adverse events occurred in one patient who had two sensors inserted. The

first attempt to remove the sensors was unsuccessful. A second attempt was made 2 weeks later using ultrasound to help find the sensors, but this was also unsuccessful. A general surgeon was able to remove the two sensors using local anesthesia.

In the third event, while preparing to remove a sensor from a patient, the investigator could not locate the sensor by palpating the area of the arm where the sensor was inserted. The investigator did not attempt to remove the sensor, and instead, a general surgeon was used to perform the removal, which was successful.

In the PRECISION study, Senseonics included an assessment to the level of systemic exposure to dexamethasone that results from use of the Eversense system. Systemic exposure was assessed by measuring dexamethasone concentration in plasma.

The eight study participants who had one sensor inserted had blood drawn at specified intervals after sensor insertion. Blood samples were collected after sensor insertion at 30 minutes, 2 hours, and 4 hours, and then each day for 9 additional days. Blood samples were then collected at each in-clinic session through Day 90.

The remaining 27 study participants each had two sensors inserted. Participants with two sensors had blood samples collected at 2 hours post-insertion and then daily for 9 additional days and at each in-clinic session through Day 90.

All subjects with one sensor inserted had no detectable dexamethasone at any point during the study. Several subjects with two sensors inserted had detectable levels of dexamethasone on Days 1 and 2 after sensor insertion. The peak value observed was 114 pg/mL, which occurred 2 days after sensor insertion. Dexamethasone was not detected in any study participants after Day 9 through the remainder of sensor wear.

Clinical sites returned sensors to Senseonics after removal. Senseonics measured the amount of dexamethasone remaining in the silicone collars of all sensors and found that between 0.18 and 0.35 mg of dexamethasone was eluted from the silicone collar over the

90-day sensor life.

Senseonics made four design changes to the Eversense CGM system following submission of the premarket approval application. Typically, Class III devices are evaluated in their final form, and major design changes are not made following clinical and analytical studies of the device.

Senseonics has made several design changes to the components of the Eversense CGM system since submitting their PMA. Changes have been made to the following components of the Eversense system: the glucose determination algorithm, the transmitter, the sensor end cap, and the blunt dissector insertion tool.

One of the modified components is the glucose determination algorithm. The glucose determination algorithm is a software component installed on the transmitter. It is responsible for converting the fluorescence measurements made by the sensor into glucose values. Changes to the glucose determination algorithm directly affect system output performance.

The PRECISE II and PRECISION studies were conducted using the original version of the glucose determination algorithm. Senseonics refers to this as the study software version of the algorithm.

After completing both studies, Senseonics finished development on a new version of their glucose determination algorithm. This new algorithm was developed on an independent set of clinical data, their European pivotal study dataset. Senseonics refers to the new algorithm as the Software 602 version. Senseonics has used their new algorithm to reprocess the raw data obtained during these two clinical studies and to obtain a new set of performance results for each study.

Senseonics is proposing to use the results obtained through post hoc analyses of study data using their new algorithm to support approval of the Eversense CGM system and

that this new performance data will be presented in labeling.

Senseonics states that the raw sensor data recorded during the clinical studies is independent of the glucose determination algorithm that is used during the study. This means that the new set of performance results that has been calculated should be the same results that would have been obtained if the studies had been conducted using the new algorithm.

Senseonics states that the new algorithm was developed using clinical data obtained from their European pivotal study and that data from the PRECISE II and PRECISION studies was not used for algorithm development or training. If approved, this would not be the first time that a new CGM algorithm was approved based on post hoc analyses such as this.

Here, we present data from the PRECISE II and PRECISION clinical studies, both with the original study results and the new results calculated using the new Software 602 glucose determination algorithm.

Senseonics' stated goal in developing the new algorithm was to improve performance during early sensor life and in the hypoglycemic range of operation.

This table shows a selection of data from the first day of each study. The data presented here is the rate at which the Eversense CGM system agreed with a laboratory comparator method to within 15 mg/dL or 15%, depending on whether the blood glucose measurement was below or above 80 mg/dL. The numbers in parentheses in each cell are the number of CGM values that agreed with comparator measurements divided by the total number of paired comparator values in each glucose range. For example, on Day 1 of the PRECISE study where the study software algorithm is used, there were a total of 20 paired comparator values in the range of 40 to 60 mg/dL, and for 12 of those measurements, the paired CGM values were within 15 mg/dL of the comparator. When the Software 602 algorithm is used, there are a total of 27 valid paired comparator values in this range, and

for 26 of them, the paired CGM values were within 15 mg/dL.

This table is an example of the performance data that Senseonics has proposed to support the approval of the Eversense system. This data is the result of post hoc processing of the PRECISE II clinical data using the new glucose determination algorithm. The table shows how frequently Eversense CGM values agreed with a laboratory comparator method to within margins of 15, 20, 30, and 40% or 15, 20, 30, and 40 mg/dL, depending on whether the blood glucose measurement was above or below 80 mg/dL. The table also shows the rate at which Eversense CGM values were different from the comparator method by more than 40% or 40 mg/dL. This dataset is pooled for all four in-clinic accuracy sessions in the PRECISE II study.

There are additional tables describing the accuracy results for both PRECISE II and PRECISION using Software 602 in your Executive Summary package.

The PRECISE II study had 30-day gaps between in-clinic accuracy visits. The subsequent PRECISION study also had 30-day gaps between the in-clinic accuracy visits after Day 30.

In order to supplement the understanding of Eversense system accuracy in the time between clinic visits, Senseonics provided an analysis of SMBG data collected at home by study participants. As mentioned previously, SMBG is less accurate than the comparator method used during in-clinic visits, so this SMBG data should not be considered as representative of the Eversense system accuracy. Rather, it is intended to provide a general idea about trends in system performance over time.

From the plot presented here, it can be seen that during the PRECISION study, system performance gradually improved for the first week of sensor wear before reaching an approximate steady state.

I will now hand the presentation back over to Dr. Balsam to present the additional

system changes.

DR. BALSAM: Thank you, Dr. Yi.

A second device modification that was made was a transmitter change. Senseonics included a new design of the Eversense transmitter in the PRECISION study. Twenty-seven participants in that study wore both transmitter designs, one on each of their two arms, and accuracy and reliability data were compared at the end of the study.

Senseonics assessed the system reliability and accuracy between transmitter designs to demonstrate that the new transmitter had a similar degree of reliability and accuracy.

System reliability is assessed as the percentage of time that the system provides a glucose value, compared to the total time that the sensor is inserted and active. As an example, if the sensor was inserted for a total of 24 hours with a new glucose value being presented every 5 minutes, that would be a total of 288 CGM values. If there were only 270 CGM values that were recorded during that period, that would be a reliability of 270 divided by 288 or 94%.

Senseonics has also proposed to change the design of the sensor end cap. This design change was proposed in response to the adverse events that were observed during the PRECISE II study, which were described previously. In these two events, sensors were found to be missing end caps upon inspection, and it was assumed that the end caps were left under the skin after the removal of the sensors.

Senseonics has hypothesized that because of the end cap design, during the removal process the end cap could be grasped by the hemostat used to remove the sensor, which could break off the end cap. To reduce the chance of this happening in the future, Senseonics has redesigned the sensor end cap so that it is flush with the end of the sensor body, as pictured here.

Senseonics has not conducted any clinical studies using the new sensor design. To

validate the new design, Senseonics has performed mechanical testing to assess whether the sensor can withstand the typical forces that are applied during the removal process. Senseonics has proposed that, if approved, this new sensor would be the version to be marketed in the U.S. Senseonics has not studied this design clinically and have stated that they do not expect the design change to affect the safety or effectiveness.

Senseonics has also developed a new blunt dissector insertion tool which they have proposed to market in the U.S., if approved. The blunt dissector is one of the tools that is used by the physician to perform the sensor insertion procedure.

The original blunt dissector, pictured here, is the tool that has been used in all clinical studies, to date, for which the FDA has seen results. This includes the PRECISE II U.S. pivotal study, the PRECISION study, as well as the European pivotal study.

The design has been updated to include two plastic guide rods on either side of and slightly above the metal dissector tip, as shown. The plastic base of the dissector has been lengthened to provide a physical depth stop. Senseonics states that the reason for this redesign is to reduce the chance of physicians implanting the Eversense sensor too deep, making later removal difficult.

The original blunt dissector design was used in the European pivotal study as well as the two U.S. pivotal studies. As discussed previously, there were four events in the two U.S. studies where investigators had difficulty removing sensors and a general surgeon was required for successful removal of sensors. There was also one additional case observed in the European pivotal study.

Senseonics has proposed that this type of adverse event is associated with the sensors being inserted too deep. The design of the new blunt dissector, with the addition of the two depth guards, is intended to limit the depth at which a sensor can be implanted.

To validate the design of the new blunt dissector, Senseonics has conducted a study

with 16 physician participants. The participants underwent the same training that they would receive in preparation for performing insertions on patients. After training, there was a 1-hour washout period after which participants performed sensor insertions on synthetic tissue. No sensor insertions were performed on human subjects.

In the study, Senseonics judged the success of the insertion by whether sensors could be palpated after the insertion. A selection of four synthetic tissue samples were dissected so that the actual insertion depth could be measured. All inserted sensors could be successfully palpated, and the insertion depth measured for four sensors was within the recommended range of 3 to 5 mm below the skin surface.

The Agency would like feedback from the Panel on whether the validation that Senseonics has performed for these four design changes support the safe use of the modified device.

Senseonics has proposed to use two additional sources of data to support the approval of the Eversense system. These two sources are a registry of their device users in Europe and a proposed post-approval study in the U.S., if their device is approved.

The Eversense system has been marketed in Europe since 2016, and Senseonics has previously presented a summary of the data that is available from their European registry. Where applicable, the FDA can leverage data that is available from other countries.

There are several differences between the design of the Eversense system that is marketed in Europe and the device that Senseonics has proposed to market in the U.S. First, the glucose determination algorithm that is used in Europe is the original algorithm, not the new Software 602 version.

The original version of the Eversense sensor released in Europe is different than the version currently on the market there and from the version proposed for approval in the U.S. The original sensor was shorter and had the dexamethasone-eluting collar placed in

the center of the sensor, as pictured here. Approximately one-third of the data available from the European postmarket registry, or about 760 sensors, uses the first version of the sensor. The remainder of the available data, or about 1,600 sensors, is from the second version of the sensor, which was the same design that was used in the U.S. clinical studies.

The blunt dissector tool that has been used in Europe is the same version used in the clinical studies to date and not the modified version that Senseonics has proposed for approval in the U.S.

There have been no reported instances of sensor end caps missing after the sensor removal from the European registry data. However, there have been three instances in Europe where sensors broke in half during the sensor removal process.

So Senseonics has proposed to conduct a post-approval study for the Eversense system, and they have presented one proposal for this study design. The Agency would like feedback from the Panel on what types of information would be useful to collect during a post-approval study of this device, if the device were to be approved.

The Agency has several questions relating to the Eversense CGM system for the Panel to discuss. The questions will be discussed at a later point during the panel. They're included here as a reference. There are a total of seven questions. Four are for panel discussion, and three are the voting questions.

This concludes our FDA presentation. I would like to thank the Panel members and public for your attention, and I would be happy to address any questions that you may have. For the questions and the answers, I will be inviting Dr. Yi to join me at the podium.

DR. BREMER: Great. Thank you so much. I would like to thank the FDA speakers for their presentations and also all of the information that you provided the Panel prior to the meeting for our prior review.

We are running a little bit ahead of schedule, so we want to entertain questions, so

now the floor is open for anyone on the Panel to ask any clarifying questions.

Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

I have two clarifying questions for the FDA. To the best of the knowledge of the FDA, are there any implantable devices that release corticosteroids, not necessarily CGMs but any other implantable devices?

DR. YI: So there are other implantable devices, but there appear to be some differences in terms of the dose of corticosteroids as well as the frequency of like insertion of the device.

DR. LAKOS: Can you provide more data? Is it a higher dose, lower dose?

DR. YI: So, for example, implantable cardiac leads, those would basically -- much lower, a lower glucocorticoid dose, and those are intended for use for a much longer period of time.

DR. LAKOS: Thank you. My second question is regarding the post hoc analysis of the algorithm data. So can the FDA clarify whether is it the standard practice and has it been used before for other CGMs or other similar devices?

DR. BALSAM: Yes. So it's not a standard practice; the standard practice would be to evaluate the device as it would be intended to be used during the clinical studies. But as we mentioned, it has been used previously by other CGM companies to validate modifications to algorithms that have been studied in the clinic previously.

DR. LAKOS: And was the post hoc results used for labeling and was used for the approval process?

DR. BALSAM: Yeah, the way that the post hoc analysis had been used previously is similar to how it's being used here.

DR. BREMER: Dr. Grunberger.

DR. GRUNBERGER: Yes, maybe along similar lines. You mentioned that you can leverage the data available, say, from other countries. Since FDA approved other systems, CGM systems, because you don't need to verify calibration, does that previous approval for different devices play a role when you try to come up with determination for this one?

DR. LIAS: No, this device has to stand on its own. When we receive an application for premarket approval, it's not a comparison decision, though we certainly can take into account the current environment. But, for today, we have to make a decision on the file presented to us, which is this device with this intended use.

DR. BREMER: Dr. Gregg and then Dr. Wyne.

DR. GREGG: Sure. I had some questions about the performance in the hypoglycemic range. Some of the tables that are presented as background material suggest that when the comparator has a glucose value under 60, that the sensitivity detection of that can be poor, in some cases 50%. Now, I realize, in some of these cases, that may be just based on one or two or just a few, a very small sample size, and it's also a bit difficult to interpret because in some cases we have YSI as a comparator and other cases a laboratory.

But I'm wondering whether -- it appears, from what you presented, that the new algorithm improved that situation, improved that sensitivity, but I'm not sure, and I'm wondering if you could comment on that. And, you know, we're -- if we're going to sort of look at the best current data on performance in that low -- in the hypoglycemic range, where should we look?

DR. BALSAM: Thanks. First, a clarification -- and for the people taking notes, this is Dr. Balsam. First, a clarification: You mentioned a distinction between the laboratory method and the YSI. So if there was any confusion about that in the tables we presented, I apologize for that, but that's the same reference. What we refer to as the laboratory method was the YSI method. And I'm sorry, what was the second part of your question?

DR. GREGG: The second question had to do with what the new algorithm does to that sensitivity against the comparator.

DR. BALSAM: Sure. So the tables that we provided, you know, we're hoping to get some feedback from the Panel on your view of what the effect of the change was. If you're talking about sensitivity specifically, in sort of a rigorous definition, that's something I would probably defer to Senseonics to respond to, but we would prefer not to comment specifically on our views of what the tables show. But, sorry, as an aside, because they are requesting approval for the Software 602 version of the algorithm, the recommendation is for you to review the tables that are for the Software 602 version of the system.

DR. GREGG: Sure. I guess what I'm trying to move towards is sort of what's our best estimate of what the false negative rate is going to be in the circumstance of serious hypoglycemia or --

DR. LIAS: When you use the term "false negative," do you mean alert rate or do you mean falsely low values?

DR. GREGG: Well, I guess --

DR. LIAS: Or falsely high values?

DR. GREGG: Sure. Or if the alert is essentially missing. I'm not so concerned about a false positive; in other words, the alert going off when the value is not low, but rather the other situation --

DR. LIAS: Right.

DR. GREGG: -- wherein the alert misses.

DR. LIAS: This is Courtney Lias.

DR. GREGG: Yeah.

DR. LIAS: We didn't present the alert rate information, but in the Executive Summary we do present different analyses of alerts, and some of them are missed alerts,

and some of them are true alerts. So we can look in here and point you to the tables that show the alert rate you're interested in. I'll look at that right now.

DR. BREMER: Great. Dr. Wyne.

DR. WYNE: So I had several questions, but one is just a comment related to your question about the alerts, and this is what I was asking earlier. So the low alert is set at 60, and I was very concerned about the accuracy below 60, but knowing that the low alert can't be set any lower and cannot be turned off, to me, that was somewhat reassuring to know that.

My questions were several. One, when you presented the data on interferents, specifically looking at tetracycline, mannitol, sorbitol, and I look at the package insert and it basically says don't use this while receiving these medications, is there any data on duration? In other words, if I take 10 days of tetracycline, should I continue to not use it for another 3 days or 7 days? Do we have any idea or any way to extrapolate from the lifetime of these different agents?

DR. BALSAM: So I think the short answer to your question is no, there is not data to be able to answer that question, mostly because of how the assessment of interference was done. It was done in vitro --

DR. WYNE: Yeah.

DR. BALSAM: -- so not in human subjects.

DR. WYNE: But this is a question patients will ask. Well, the last dose of tetracycline is the last day that I worry, and even so, I get in the hospital, you know, how long do we have to wait before we can resume using it?

DR. BALSAM: Yeah. So this is related to one of the specific discussion questions that we have --

DR. WYNE: Okay.

DR. BALSAM: -- for the Panel, which is essentially the sufficiency of the labeling mitigation --

DR. WYNE: Okay.

DR. BALSAM: -- as it currently is. But if there's anything particular to that that Senseonics would like to add, they're welcome to do so.

DR. GOODNOW: Thank you. I very much understand the question, and appropriate. We have not studied specifically, but obviously, the pharmacology, the half-life of tetracycline is well understood, and we would certainly be willing to work with the Agency to modify the labeling to include that, because you're absolutely right, they'd like to know when can I get back to using my CGM?

DR. WYNE: Yeah.

DR. GOODNOW: Certainly.

DR. WYNE: Yeah, I figured I could go look it up, but you know, when I'm in the clinic and a patient's asking me, I don't really have access to that data.

DR. GOODNOW: No, no, that's our responsibility, not yours.

DR. WYNE: So my other two questions, so fairly quick: You mentioned, in your presentation, there were three devices in Europe that broke on removal. Do you know if the breakage occurred on removal at 90 days or between 90 to 180 days?

DR. BALSAM: Yeah. So the referenced study in Europe, that was -- the reference data in Europe where they actually broke in half, that was during the -- that was the on-market use of the device, and I think only 10 of those sensors in the whole 1,600 were the 180-day version. So it's my understanding, and Senseonics can correct me if I'm wrong, but those would have been the 90-day version of the sensor.

DR. WYNE: Okay, so not past 90 days when they broke?

DR. BALSAM: Correct.

DR. WYNE: So, within the time frame that we're using it, okay.

DR. BALSAM: Correct.

DR. WYNE: My other last question, this is just to clarify for me because I was looking at the calibration and then it talked about dosing decisions. This request is for adjunctive use, not for non-adjunctive use, meaning patients still need to finger stick to dose for meals?

DR. BALSAM: Correct.

DR. WYNE: Okay, thank you.

DR. BREMER: Dr. Tung and then Dr. Kraft.

DR. TUNG: Can the FDA describe a little bit more about software changes between 601 and 602, particularly with a look towards whether there will, in the future, be a 603? How would that be handled?

DR. BALSAM: Sure. So, in the interest of not discussing what may be proprietary information, I'll defer to Senseonics for any technical discussion. But yeah, at a high level, there was a change in how the software handles the calculation of the glucose. If Senseonics would like to provide any lower-level details, I'll defer to them on that as far as any plans for future development.

DR. BREMER: Please.

DR. JAIN: So, talking about the current -- the study software and the current version, the difference was in two periods, as we talked about, the early wear period, which is after Day 1 and after Day 1, and then the hypoglycemic range. And as Dr. Balsam mentioned, without getting into the details, what we did is looked at how we reacted the calibration and worked with the best scheme that is possible to calibrate against for the early wear period. And for hypoglycemic, we took more into account the lag, how we compensate for the lag and how we look at the physiological responses when you do go into the low ranges.

As far as the future goes, there are many other enhancements that we continue to make, and I believe, as we submit, we'll try to make sure we give them the right amount of information every time for them to make the right decisions.

DR. BREMER: Dr. Kraft and then Dr. Grunberger.

DR. KRAFT: This is Walter Kraft.

So I want to thank you for the richness of the data that you provided, primarily around high and low values. In clinical practice, oftentimes it's the vector and the rate of change which are very helpful for the patients to manage their sugar. So the question is are there any established metrics for both the vector and the rate of change for other continuous glucose monitoring devices?

DR. YI: Well, I mean, right now there's no, like, guidelines in terms of how to specifically use those metrics clinically. And just to point out that in the PRECISE II study, the study participants were blinded, so they could not see any output from the CGM device, but in the PRECISION study, the subjects were able to see the results of the CGM readings as well as alerts and rate of change.

DR. BREMER: Dr. Grunberger and then Dr. Wyne.

DR. GRUNBERGER: Yeah, so a quick question. Did FDA have access to any data on the performance of the sensor versus the number of calibrations, i.e., what happened to patients that didn't calibrate versus patients who calibrated four times a day or more?

DR. BALSAM: So, early on in the review process, Senseonics did provide some analysis based on, again, a post hoc analysis of if subjects used two calibrations versus one calibration; that information hasn't been used in the review here because what they're requesting is approval for a device that requires two calibrations per day. Does that answer your question?

DR. GRUNBERGER: I was wondering if the Sponsor actually knows anything about

that, because you know what's going to happen; if it's approved, the patients will do different things.

DR. BALSAM: Yeah. As far as the requirements for exactly how frequently the system must be calibrated before it will blind itself, I would defer to Senseonics if you want some information on that.

DR. GOODNOW: Thank you. The device is fairly well constrained in regard to calibration. The two calibrations per day are required. There is a fairly generous window of approximately 10 to 16 hours, but if the device is not calibrated in that 16-hour time period, then you will not continue to get glucose results. So we're pretty onerous to protecting accuracy of the system, which we believe is the most important. So the data characterization frankly is we could only synthetically do because patients will calibrate this device twice a day or not get results.

DR. BREMER: Dr. Lias.

DR. LIAS: Courtney Lias.

I have a clarification for Dr. Gregg's question on the alerts. So the alert performance for the different software versions, in the appendices, Appendix 1 and Appendix 3 have the PRECISE II information in Tables 21 and 22, so you can compare those to each other, and Appendix 2 and 4 and Tables 29 and 30 have the alert performance. In the background section, looking at the alerts, it describes what each of those columns, what type of alert each of those columns are.

DR. BREMER: Thank you, Dr. Lias.

Dr. Wyne.

DR. WYNE: I actually just wanted to comment to your question on guidance with respect to the arrows, and I went to look up this paper and, of course, immediately lost my wifi access. But there's a paper recently published, I believe it was from the Endocrine

Society, with some recommendations on how to start to apply the arrows in real life and calculations that could be used as a guidance to use trend arrows. Now, that's not based on the Senseonics data; it's based on experience with currently available devices. But the societies are trying to create guidance on how to use it, and it is in the peer-reviewed literature. I just can't access it at the moment.

DR. BREMER: Dr. Avery and then Dr. Lakos.

DR. TUNG: Can the FDA or Senseonics describe how visible this device is from the surface? In the hospitals, subcu heparin is often given subcu. Will it be obvious that there's a device in the way, to not give it there?

DR. BALSAM: Yeah, our understanding is that if the transmitter is not attached to the skin and if the adhesive patch hasn't remained on the skin, visibility of the sensor itself beneath the skin is minimal. As far as we know -- anyone with practical experience, again, I'd have to defer to Senseonics on that.

DR. GOODNOW: As you noted -- could we just have a photo of the transmitter? That we do, obviously, believe is obvious. Without the transmitter, and this is not -- excuse me. This is actually a photo of 90 days after the insertion, so I apologize. In this particular photo, the actual sensor is not there itself, but it is -- it would not typically be visible without the transmitter in place, the sensor in place. I think, at each one of your places, there was devices. You could see that it's fairly small, it's about a 3 mm by 18 mm rod, so it's quite small and generally palpable but not visible on its own.

DR. BREMER: Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

My question is related to the redesigned end caps, and I'm assuming both the original and the improved design has undergone, in fact, design verification, and during the design verification, the sensor was subjected to physical force and other issues. So if both

passed, were the accepted criteria different that pushed the bar higher for the redesigned cap, or how can we make sure, based on the available results, that the redesigned cap will be more resistant?

DR. BALSAM: Thanks, that's a good question. Our understanding is that the original design verification and validation procedures did not specifically include an assessment of the compressive forces or the shearing forces that would be exerted directly on the end cap. For the new sensor design, as part of the verification and validation process, there were specific assessments done to apply, you know, the types of compressive and torsional forces that you would expect from grasping the sensor with a hemostat. And if you need any more details about it, again, I'll turn it over to Senseonics.

DR. LAKOS: Just to rephrase to make sure I understand, so the original design verification did not include the physical force type of testing?

DR. BALSAM: I'll defer to Senseonics on specifically what was done. Yeah, my understanding is that there were tests that were added to specifically test the new design of the sensor against that type of force.

DR. JAIN: Thank you. That is correct. When we initially designed it, we did not have a compressive force requirement or a torque requirement. It was during the PMA review that the requirement was put in place, and the new design meets that requirement.

DR. BREMER: Dr. Grunberger.

DR. GRUNBERGER: Yes, thank you. I know this is getting maybe a little a bit ahead of the game, but in the proposed package insert, it talks about the interference with MRI, and it says that you should contact your physician before an MRI and arrange for sensor removal. I'm just trying to figure out how this would play out in a situation which you don't have much of a choice about MRI.

DR. BALSAM: Yeah. So I think that the way that the system is currently

contraindicated for MRI is similar to how other similar systems, where you have implantable devices that wouldn't be readily visible from the exterior, how risks are mitigated for those devices. Senseonics mentioned that, you know, people are encouraged to have -- carry a card in their wallet to indicate that they have a device that's implanted. Other than that, the risks seem to be similar as far as the detectability in the event that person, say, is brought unconscious to a hospital and subjected to an MRI. Does that address the question or --

DR. GRUNBERGER: No -- it does. But, again, this is different because it says you're supposed to contact your physician and arrange for removal of the sensor first. So I'm just trying to -- so thanks for the logistics of that.

DR. LIAS: I'd just like to clarify. I believe Dr. Balsam meant that it's similar to other implanted devices, not other CGM devices.

DR. GRUNBERGER: And I understand, but I was wondering. So what is the worst-case scenario?

DR. LIAS: Yeah, we would actually -- if you have feedback on this point, we would like to understand any concerns the Panel might have.

DR. BREMER: Dr. Rendell and then Dr. Tung.

DR. RENDELL: Has FDA reviewed its safety data on other subcutaneously inserted devices? So, for example, subcutaneous exenatide, in terms of scarring, skin infections, other such issues?

DR. BALSAM: Similar devices rarely come through the Office of In Vitro Diagnostics. In our review of this device, we did some comparative assessments of devices that are on the market. You asked specifically about skin infection. From our review, they seem to be comparable, but it's something that we would like feedback from the Panel. Based on the rates of infection and other complications that Senseonics has presented, if you have any

specific feedback on that.

DR. RENDELL: And, in particular, long-term scarring.

DR. BALSAM: Yes. So long-term scarring or rather the effects of repeat insertions -- you know, potentially the device would be used indefinitely -- that's a specific question that we have for the Panel to discuss later.

DR. RENDELL: Thank you.

DR. BREMER: Okay, Dr. Tung and then Ms. McCollister-Slipp.

DR. TUNG: In the FDA Executive Summary, it says a thin layer of platinum covers the entire surface of the sensor. Does the FDA believe that platinum toxicity is an issue in this case?

DR. BALSAM: So there was a biocompatibility assessment that was performed, and platinum toxicity, from our perspective, was not a concern. If anyone on the Panel has any input on that, we'd be interested in hearing it.

DR. BREMER: Ms. McCollister-Slipp.

MS. McCOLLISTER-SLIPP: My question is similar to Dr. Grunberger's in that I'm trying to understand this, and it just may be my ignorance, but in terms of -- so if I am, you know, hit by a truck and taken to the hospital and I need an MRI, I don't have a diabetes card, I always kind of counted on the fact that if they don't figure out that I have diabetes because of my insulin pump, then I probably have bigger issues, but I mean, what is the safety risks? So if I am put in there -- and I don't know if we know this, but I would like to know if we know this. So if I'm put into an MRI with the sensor in, is there a safety risk, or is it a risk of malfunction? Or do we know that?

DR. BALSAM: Yeah, sure. So the information that we have, we have not seen any direct assessment of exposure to MRI when the device is in use. So the short answer is we don't know. Medtronic -- I mean, not Medtronic. Senseonics has proposed to, you know, a

labeling contraindication that has been discussed, and if there's feedback from people on the Panel who have experience with similar devices with similar types of risk, we would be very much interested in hearing what your opinion is of the adequacy of the proposed MRI contraindication.

DR. LIAS: That's right. And the expectation is that there might be burns; you could have burns because of the external energy introduced.

MS. McCOLLISTER-SLIPP: Do we know from any other, like, other types of devices, like from, you know --

DR. LIAS: There's also a magnetic component.

MS. McCOLLISTER-SLIPP: -- defibrillators or anything like that?

DR. LIAS: Yes, this is a general issue that comes up with many types of implanted devices, and so depending on the size of the device, where it's placed in the body, but both the electrical energy and also the magnetic energy introduced can cause some challenges with the electronics in terms of actual physical harm to the patient, and the magnitude of harm depends on the specific device. I don't know whether Senseonics has any additional comment or information on the potential risks.

DR. JAIN: So this is information, as Dr. Balsam pointed out, we haven't submitted yet. We are working on it. We understand that it could present itself in an emergency situation. In most cases, you would have a device, which is the transmitter on your arm, that would indicate something is going on. On the back of the transmitter is the Eversense and company information. However, we understand the gravity of it. Talking about the two things that MRI could affect is displacement or the torque, or the heating. So we have done those two assessments with a 3 T machine already, and again, not evaluated by FDA. This is us presenting where we are currently. We have that data, which makes us comfortable with it, that there is no safety risk to the patient. However, our priority is to go

complete the testing per the standards and submit that so we can get that contraindication off later.

MS. McCOLLISTER-SLIPP: Understanding that, I mean, one thing that I would think that we might -- maybe when we talk about this later, but as somebody who has a lot of doctors' appointments, does lots of tests, if I have to go to the doctor, if I go to the doctor and he says you need an MRI and I had just gotten this inserted 2 weeks ago, and then before I get the MRI, I have to go to the endocrinologist to have this taken out, I mean, I'm assuming that that would be the procedure then, that it would -- and then I would have to get it reinserted after the MRI?

DR. JAIN: That is the right procedure for the labeling. Yes, it's contraindicated.

DR. BREMER: Dr. Tung and then Dr. Wyne.

DR. TUNG: I guess I'll say we have some experience in anesthesia with devices of this sort because we will sometimes place epidural catheters that then patients get MRI for the bleeding consequences thereof, you know. And in addition to the heating, there's also torque on the catheter from the catheter actually moving in the magnetic field and then the ability of the catheter or the device to distort images that are directly adjacent to what you're looking at. I imagine that if this device moves, then it may go back to its immediate insertion phase and so the accuracy may not be as good. I can imagine that might be an issue.

DR. BREMER: Dr. Wyne.

DR. WYNE: You know, it's interesting because one of the things you guys are basically raising is part of the training and planning; it isn't just you're going to come back in 3 months and I'm going to take it out. But my office has to have a mechanism that if you need emergency removal, we're going to agree to see you immediately and take it out. And I can even envision, in the hospital, emergently removing it for Dr. Tung because he needs

to do something. But you're absolutely right, we need to -- and I assume we'll do it this afternoon -- discuss the risk of emergent MR or CT and is that worth the risk.

My question is actually something a little bit different, thinking when someone is asking about are there other implants. So we will have a lot of young adult women with Type 1 and Type 2 diabetes, and they often have implants for birth control. Now, do we have any data on whether there's going to be an interference with those implants or even a suggestion of how far away that this should be from those? Do we know anything or have any suggestions?

DR. BALSAM: So, again, the interference testing that was done was all in vitro, you know, bench-type testing. My understanding is there's not specific testing that has been done that would answer the question as far as, you know, specific placement near or, you know, a recommendation for how far away it should be from other implanted devices.

As far as specific interference for the drugs that would be in those subcutaneous devices, I don't believe that any of the 41 substances was -- well, yeah, was any common birth control, so that, I believe, has not been assessed. Again, this is something that if the Panel thinks is an important point to discuss, we would welcome hearing about it.

DR. WYNE: Yeah. No, I just asked it because I don't think -- chemically, I can't think of a reason why there would be a chemical interference, but there's probably a logistical issue, and those devices are usually implanted for at least 3 years, I think. So it's something, you know, if we're supposed to be alternating arms, we need to be cognizant that they're there and we're not the person, the endocrinologist isn't the person implanting those.

DR. BREMER: Dr. Burr.

DR. BURR: Yeah, Bob Burr.

There must be some postmarketing experience that Senseonics has. It's inevitable

that somebody has had an MRI with one of these things in. Are you guys aware of any case reports, anything you guys have received, adverse reaction reports of these sensors in an MRI setting? It's simply inevitable that it's happened.

DR. KELLEY: So, yes, we do have experience in the European setting of patients who required emergent MRI, and to your point about three things, movement, temperature excursion, and functionality, and we have had patients undergo MRIs, we've talked about the distortion ability and artifact, and those patients have successfully undergone MRI, and the sensors worked well with no accuracy issues post-MRI.

DR. BURR: So the experience would suggest that it's actually benign?

DR. KELLEY: Again, our label indication is such that we need to make sure that we're doing the appropriate studies for a submission that has not been included yet.

DR. BURR: Right, but there's no experience out there that would suggest that this would be --

DR. KELLEY: Our limited European experience with some emergent cases -- because I get the phone calls in the middle of the night that say it's 5 o'clock in the morning and you're up and we need something -- our experience would suggest that it's benign.

DR. BURR: Oh, okay. Okay.

MS. McCOLLISTER-SLIPP: And how many of -- and, again, I know that this is not on your label at this point, but it is an important issue if it's going to be out there. How many patients have you seen who had an MRI with the device in, in Europe?

DR. KELLEY: Under 10 but more than 5.

MS. McCOLLISTER-SLIPP: And there were no issues, no safety, no burns, no --

DR. KELLEY: None whatsoever.

DR. BREMER: Dr. Kraft.

DR. KRAFT: So Walter Kraft.

So we heard about some of the devices breaking on removal, so the question specifically is around toxicology, both about the mass of the fluorescent pigment and then if there is the requirements from the FDA, in terms of toxicology, for any internal components.

DR. BALSAM: Yeah. So this is a specific item that we would like to hear feedback from the Panel. In the cases in the U.S. studies and the one European study where the sensor end cap was broken off, our understanding is that all of the materials that would have been exposed are things that had been previously assessed and found to be appropriate for continuous exposure. In the three cases where, in the European postmarket space, where sensors broke in half during the explant procedure, our understanding is that the internal components of the device that would likely have been exposed then have not been assessed for biocompatibility, and it's an area that we're interested in hearing feedback from the Panel, if you have it to give.

DR. BREMER: Is it okay with the FDA to get some clarification?

DR. GOODNOW: Sure, just clarification on a couple of things. From a toxicity perspective, all of the components, internal as well as external, have been tested and have been shown by 10993-1 as being long-term implant compliant. As part of that testing, you do actually grind up any of the implant material, and all of that is characterized as well. So that testing is available.

From a breakage perspective, there are two issues. There's the end cap removal that we've talked about. The other three cases are actually breakage of the sensor during removal. Those appear to be related to the selection of hemostats with a very high compressive force. So as part of our learning and changing, we actually have changed in Europe such that we now provide a particular hemostat for removal, so we've tried to limit that, any ability to actually crush it. I would anticipate that we would provide kits as well in

the United States with a prepackaged, specific analyzed hemostat.

DR. BREMER: Thank you. Are there any further questions from the Panel for the FDA?

(No response.)

DR. BREMER: I want to once again thank the FDA for all the information you provided in your presentations. And we are 15 minutes ahead of schedule, and I'm going to make a gut call, if that's okay with you, not to break early for lunch. I know a lot of people have traveled to participate in the open public discussion, and so if people will bear with me, I would like to start. I have a couple of administrative things to read beforehand, but we will go ahead and start with the open comments portion of the program. We will resume with that at 1 o'clock, but again, I know people -- a lot of people have come and a lot of people would like to speak. So if you'll bear with me, I will -- if that's okay with you.

(Off microphone response.)

DR. BREMER: Oh, I'm going to turn the floor over to Commander Garcia.

CDR GARCIA: Thank you, Dr. Bremer. I just want to piggyback on your comments.

And if your name is called and you're not here, we will call your name again at 1 o'clock because we are scheduled to speak at 1 o'clock.

I will now read the public hearing disclosure.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, 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 for 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 have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The insights and comments provided from the public to FDA and this Panel is for consideration on the topic of this meeting and are highly valued. One of the goals for today for this Open Public Hearing is to conduct fair and open presentations. Each registered speaker has been given 3 minutes to address the Panel. We ask that you observe the 3-minute time limit. The lights on the podium indicate when your time is about to expire. Yellow means 30 seconds, and red means your time has expired. We ask that each presenter speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates each speaker remaining cognizant of their speaking time. Thank you in advance for this consideration.

Dr. Bremer.

DR. BREMER: Thank you, Commander Garcia.

For the record and for the transcriptionist, we currently have 19 speaker requests for today's meeting. Again, we thank you for starting early. We do want to hear from you, but each scheduled speaker, as Commander Garcia said, has 3 minutes to advise the Panel. If I call your name and you're not here at the time, you will not be penalized. We'll resume at 1:00 p.m.

The first speaker for the Open Public Hearing is Dr. Mark Christiansen.

DR. CHRISTIANSEN: Good morning, I'm Mark Christiansen. I'm an endocrinologist with 20 years of experience in clinical research, the last 9 in drug and device studies, and I participated in both of the U.S. Senseonics studies. My travel expenses and lodging are

being covered but not my time.

I wish to share with you my impression of the device that you're now considering. As an endocrinologist, I perform few procedures, but I was able to quickly learn how to insert and remove the sensor without difficulty. It takes approximately 5 minutes, including the time for the anesthesia to take effect. And I have seen and used the new insertion device, and I think that it will help to limit the deeper insertion of these sensors. The removal takes less than 10 minutes in almost all cases, and it's my belief that the small incision is quite acceptable to all of the patients with whom I've worked. More importantly, my patients' experiences have been positive. Many are veterans in the use of CGM and have benefited from them.

The accuracy of this device has been presented earlier and is comparable to the devices already approved. However, a few features of the Senseonics device stand out to my patients. First, the daily application of the transmitter is easily learned and perfected. I'm not aware of any of my patients who were not able to perfect this. Secondly, the twice daily calibrations was not an impediment to its successful use either.

Number two, there were no dermatologic complications after daily application of the adhesive in the same area. This possibility had concerned me but did not occur. Although the protocol required daily wear of the transmitter, patients recognized that they could take off the transmitter temporarily without throwing away a perfectly good sensor. This is a dilemma which does arise for patients using the currently available sensors. Patients also noted that they did not have the bruising and minor scars that were associated with replacing the sensor every week.

Third, patients can interact with the information a bit more easily than with currently available CGM. Being able to view today's trend in blood glucose is very helpful to my patients who use the CGMs, and Senseonics is no different. However, they can also look

at their device and see trends of the last several days without needing to upload the device either to the cloud or to a program.

Fourth, the experience of many but not all patients on the first day of use shows that the accuracy of any device can be a little lacking, and it improves. And while Senseonics has shown that their device improves with time, patients experience 90 days of accurate results.

Thank you.

DR. BREMER: Thank you. Operationally moving forward, what I would like to do is call the next speaker and the speaker after that. If I call your name, if you could raise your hand so I know you're in the audience, it may facilitate just getting through the list of people who want to speak.

Next on the agenda is Julia Wedel, and following Ms. Wedel is Randy Schaaf. Are both here?

Julia.

MS. WEDEL: Okay. My name is Julia Wedel. I'm from Berlin, Germany. My travel is reimbursed by Senseonics. And I'm 32 years old, and I have diabetes since 2010. So I'm a patient, and I have my sixth sensor now.

First of all, I'd like to talk about the inserting and the removal procedure. In general, I've made good experiences while inserting and removing the sensor. It's a very short process. It takes approximately 10 minutes in total. Yes. Actually, the injection of the anesthesia hurts the most. After that, I've had no pain. So all insertions and removals were successful. And what I really like is that you can see only a little cut, as we have seen on the pictures before.

Now, I'd like to speak about the advantages of the Eversense system in comparison to other CGMs. For me, it's very comfortable that the sensor stays a long time under the

skin because all of the other systems need to replace every 1 to 2 weeks. Totally, because when you have diabetes, you have to take care of a lot of things anyway, such as insulin pump, normal measurements, batteries, etc.

The second advantage for me is the patch with the transmitter peels off because, yes, you hit the transmitter so you can just take another patch in case of replacing the sensor.

In addition, I'm more flexible with the Eversense system. If I like, I can take the transmitter off for special clothes such as evening dress, summer dress, or when I take a bath, for example.

Furthermore, I have less skin irritations in comparison to other CGMs. This is why, with other systems I tried, you need to have a new sensor.

What I also prefer is that I don't need an extra handheld device for the monitoring, to display the glucose data. I can see my measurements directly on the mobile phone, which I have usually with me. It's very comfortable for me and -- no, what is very comfortable for me is also use during meetings at work, because it is very discreet.

Yeah, all in all, it can be said that I have only my good experiences with the system. It's easy to handle, and for me, it's the evolution of CGMs.

Thank you.

DR. BREMER: Thank you. Is Mr. Randy Schaaf in the audience, or is he waiting?

(No response.)

DR. BREMER: Okay, the next speaker will be Ms. Lisa Powell from Pleasant Hill, California, and after Ms. Powell is Dr. Katharine Barnard.

DR. EDELMAN: I'm not Lisa Powell, but I was just asked literally 30 minutes ago if I would read it for Lisa as she couldn't make it here today. She was a patient, as I understand it, I've never met her, but she was a patient in one of the Eversense studies and under the

auspices of Mark Christiansen. And I'm just going to read verbatim. And I also have Type 1 diabetes, so as I read this once a few a minutes ago, it was very heartfelt. Okay.

"My name is Lisa Powell, and I was diagnosed with Type 1 diabetes at age 5. I was in my second week of kindergarten in 1967 when I was sent to Children's Hospital for 2 weeks. While I was in the hospital, the doctors told my parents that I would only live to the age of 20. I can't imagine hearing that news about your child. My mother didn't tell me until 5 years ago on my 50th birthday. I was one of those people who had a Clinitest kit and has to pee in a Dixie cup every day, 5 drops urine, 10 drops water, drop the pill in, and pray it didn't turn orange.

"It's not lost on me that companies like Senseonics are the reason I'm still here. It's companies like this that decided Type 1 diabetes is not going to be a death sentence. I've not only outlived my expiration date by 30 years, I also have two amazing healthy kids.

"I have had the great fortune to have endocrinologists over the years who taught me how to use information to make decisions about my own diabetes care. They gave me the power to take care of myself, but to do that, I need information at my fingertips, and this was the amazing thing about the Eversense CGM; the information was right there. It was intuitive, easy to understand, and easy to put to use. No uploading, no downloading, in real time.

"I never would've imagined that a pie chart could change my life, but it did. Being able to see a chart comparing my percentages of in range, above range, and below range was inspiring. The pie chart gave me a goal to work towards, and using the other statistics on the Eversense, I got that chart to look just the way I wanted.

"I was not thrilled with the Eversense at first. I didn't think I would last the first 30 days. But once we got to know each other, I came to love the Eversense. I especially liked how the transmitter would vibrate if I went low, just a subtle reminder like, hey, you might

want to do something about this. I cried all over one of the engineers the day I had to give it back because the Eversense had become my trusted partner. I am grateful to Eversense for working towards the reality of giving people with Type 1 diabetes the power to make informed decisions about their own care. I would not hesitate to use the Eversense again, and I hope to have that opportunity."

Thank you.

DR. BREMER: Thank you. And thank you for filling in for Ms. Powell.

We'll have one more speaker this morning, and then I have a few operational questions before lunch. So Dr. Katharine Barnard from the UK.

DR. BARNARD: Hi. So I am Professor Katharine Barnard. I'm a health psychologist. My disclosures are that I have received research funding and travel expenses from Roche, Novo Nordisk, Ascensia, Sanofi, Senseonics, and the NIHR.

I'm here to present an evidence-based -- perspective based on professional expertise and the research that my team and I have conducted.

As we move increasingly towards timely glycemic range as a primary marker for glycemic control, it is crucial that CGM devices meet user needs. These needs include psychosocial functioning and lift experience alongside medical outcomes. An individual will only benefit from a medical device if they are able to incorporate it into their daily lives. Devices must be discreet, reliable, and sufficiently flexible to meet the needs of each user.

And it has long been recognized that disease treatments, as well as the disease itself, can negatively impact on quality of life. Health-related quality of life, according to the World Health Organization, consists of physical health, psychological, independence, social relationships, and environment. The implantable CGM addresses four of these domains: physical health to improve glycemic control; psychological health to reduce worry, fear of hypoglycemia and increased confidence and well-being; independence by reducing reliance

on others and lift one's anxieties; and social relationships by reducing the burden on diabetes-related distress of family members and cares associated with hypoglycemia, hyperglycemia, and erratic numbers.

Our research as an adjunct to the PRECISE clinical trial, and more broadly in developing and assessing PROs associated with diabetes medical devices, clearly demonstrates a positive impact on psychosocial functioning and quality of life. Our participants have reported a high level of user satisfaction for the implantable device, particularly in terms of being safe while sleeping and more confidence about avoiding serious hypoglycemia. They benefit from the discreet control the device offers through a handheld controller and removal sensor transmitter without pain and cost of lost sensor use experience with other systems.

Safety is obviously a key concern for people with diabetes and their family members, and 73% of participants in the trial felt more safe in their diabetes management using this device. These results correspond to a significant improvement in A1c.

Furthermore, the longer duration of sensor life reduced the burden of self-management. With replacement every 90 days, most participants would choose to be inserted again, and 93% report reduced burden of daily use with the device. It's always difficult, as a researcher, to have to take back a device that participants want to keep.

In summary, there is an urgent need for accurate, reliable, enduring, and discreet CGM devices to support optimal self-management. In terms of glycemic control and psychosocial burden, and I cannot stress the quality of life impact enough, this device appears to be a step forward in that regard.

Thank you.

DR. BREMER: Thank you, Dr. Barnard.

Okay, operationally, I now think we're going to break for lunch so everyone gets

some sustenance. I want to thank everyone, the panelists, all the discussions, the audience, for a wonderful morning. Before you go, let me read some disclosures.

Particularly those on the Panel, please do not discuss any aspect of the meeting topic during lunch among yourselves or with any members of the audience. For everyone, we will resume promptly at 1:00. Again, I do want to give everyone an opportunity to say what they want to say, especially those who signed up. I will ask everyone to return on time. I will start right at 1:00, particularly those on the Panel.

Other operational issues: Everyone must vacate the room from noon to 1:00 p.m. That includes us on the Panel. All personal belongings, everything, the room will be secured by the FDA, but everyone must leave. The room is off limits until 1:00 p.m. The doors will open, and we will all file in, just like in grade school, and we will resume promptly at 1:00. Thank you.

Wait, I forgot one thing. Wait. Whoa, whoa, whoa.

CDR GARCIA: For Panel members, in your folder you have a little slip of paper about lunch. There's a private room for you in the dining room. And please don't discuss your -- the contents of the meeting with anybody else. Thank you.

DR. BREMER: Thank you, Commander Garcia.

(Whereupon, at 11:59 a.m., a lunch recess was taken.)

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

(1:01 p.m.)

DR. BREMER: Operationally, it is now, according to iPhone, 1:01 and we will resume the Panel meeting. We will now proceed with the Open Public Hearing portion of the meeting that we started prior to lunch. If you weren't here prior to lunch and you missed your name, we'll circle back with you. Registered public speakers are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

And now, as before, Commander Garcia will now read the Open Public Hearing disclosure process statement.

Commander Garcia.

CDR GARCIA: Thank you, Chair.

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for this Open Public Hearing is to conduct fair and open presentations. Each registered speaker has been given 3 minutes to address the Panel. We ask that you observe the 3-minute time limit. The lights on the podium indicate when your time is about to expire. Yellow means you have 30 seconds left, and red means that your time has expired. We ask that each presenter speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates each speaker remaining cognizant of their speaking time. Thank you in advance for this consideration.

DR. BREMER: Thank you, Commander.

We have 15 speakers left in the program that have registered. Operationally, what I'll do is I'll call the speaker, and I'll also call the speaker on deck. If the individual on deck could raise your hand for me, that way I know you're here. If not, I'll just proceed in a sequential manner.

So the first speaker starting this afternoon's session will be Mr. Randy Schaaf from Lake Elsinore, California, and on deck is Mr. Tobias Schulte from Bad Vilbel, Germany.

MR. JOHNSON: Good afternoon. My name is Bennie Johnson from JDRF. I'm actually speaking on behalf of Mr. Schaaf. I don't have any financial disclosures.

"Hello, my name is Randy Schaaf, and I was a participant on the Eversense CGM study, which ran August through November last year. I can say with all honesty this was the best diabetic care device that I ever experienced in my 18 years of being a Type 1 diabetic. Using a painless transmitter in my arm, I was able to continuously monitor my blood glucose levels on an Apple iPod. I was even able to use this while I was playing sports, including softball and cycle spinning. The best part of this, however, was being able to have an alarm set in the iPod so that if I was sleeping and my blood sugar got below 60, my musically set alarm would easily wake me up. Many Type 1's have died during their sleep while their blood sugar got too low and caused numerous complications. This device will

give us peace of mind, knowing we have the ability to get alerted when low blood sugar levels could potentially kill us.

"This device is also user friendly. You need to calibrate with a regular meter two to three times daily, but this is minimal compared to testing all day and during athletic activities. You can also do analysis on this device to see when you are having highs and lows during the day and at night. I can use this to determine proper Humalog insulin injections.

"It used to be that Type 1 diabetes was known as juvenile diabetes. Not anymore. I became insulin dependent at age 45. I'm now almost 63, and the need for a device such as this has become almost mandatory. While I've never had any health complications to this point, I always worry, at this age, of what could happen. I even had a friend who was my age who just died of complications from diabetes. Having this device would really allow me the confidence and security in dealing with everyday life. There are millions of insulin-dependent diabetics that need all the help they can get from our new technological advances.

"When I was doing the research study, I was in a group with five other individuals. We ranged in age from low 20s to mid-60s. All expressed positive support for this device. I hope that FDA takes this testimony and gets the Eversense CGM approved for usage by the general public. I have tested and used many devices in my 18 years with diabetes, and this, by far, is the best device I've ever experienced. I was removed right around Thanksgiving last year, and I still miss it. I really want this back.

"Thanks for taking my testimony. Randy Schaaf."

Thank you.

DR. BREMER: Thank you. Next, we'll hear from Mr. Tobias Schulte from Bad Vilbel, Germany, and on deck is Mr. Jeff Hitchcock from West Chester, Ohio. Thank you.

MR. SCHULTE: Good afternoon. My name is Tobias Schulte from Germany. My travel expenses are paid by Senseonics.

I'm 37 years old and married. I have a 3-year-old son. I got my Type 1 diagnosis in January 2016. I'm using Eversense since 2016, and I am on my fifth sensor. It helps keep my diabetes in control in my everyday life as well as during high performance athletics. I've been involved in competitive sports since I was 6, and I've run 19 marathons, including two marathons with Eversense in the very hot desert of Dubai, and I crossed three Ironman finish lines.

Here's why I feel safe and have a good sense of well-being with Eversense system. First of all, the alarm function: I have often been in situations where I assumed my glucose values to be within the target range, but then I feel the transmitter vibrating, drawing my attention to the adverse reading, despite the fact that I was feeling fine.

Although I know that an HbA1c value is not everything, I find it easier at night to optimize my average with Eversense. In the evening, I often inject insulin and go straight to sleep. Using this technique, instead of waking up with a value of 120 the next morning, I often wake up with values between 80 and 100. If the glucose value drops too much, I am woken up by the transmitter. The device can be quite piercing, which is good because I sleep soundly.

Talking about the handling, I think it's good that I can take the transmitter off and then quickly reattach it. There are times when I'm happy to be completely free of equipment. The patches are great. I have worn over 400 so far and never have noticed the slightest side effects. They adhere well to both the skin and to the transmitter itself.

Talking over everyday life, I like being able to monitor glucose levels while driving or while cycling or when on a crowded city train. A quick glance at the watch is all that's needed.

Let's normalize. When I'm in a marathon run, I use my iWatch and Eversense to monitor my speed, my mileage parts, and of course, the glucose values. I can adjust the default settings in the app so that I get alerts if my glucose levels change abruptly while I'm running.

The focus of discussions around Eversense is often around the insertion and removal of the sensor. I can't deny that these procedures haven't left their mark, but they are small scratches rather than big cuts.

And, finally, what effect does Eversense actually have on what's going on around me? The best thing family and friends can say to me is, "Toby, with that system, no one realizes anymore that you have diabetes."

In summing up, Eversense has given me the highest level of security, the highest level of comfort, and the highest level of freedom, both in everyday life as well as in competitive sports.

Thank you very much for listening.

DR. BREMER: Thank you. Next, we have Mr. Jeff Hitchcock from West Chester, Ohio, followed by Dr. Dorothee Deiss from Berlin, Germany.

MR. HITCHCOCK: Good afternoon, my name is Jeff Hitchcock. I have paid for my travel costs myself. I am the Founder and President of Children with Diabetes, an organization that provides education and support for families living with Type 1.

In September of 1989, my daughter Marissa was diagnosed at the age of 24 months at D.C.'s Children's Hospital. Her pediatric endocrinologist taught us to measure her blood sugar and dose insulin. Back then, the best tool to measure glucose required a large hanging drop of blood and 2 minutes. Over time, that drop shrunk to a whisper and the time to seconds, with accuracy and ease of use improving as well. People with Type 1 got great tools to get the most important information they need to make the decisions for their

blood glucose levels.

When Marissa was about 13, a new technology emerged: CGM. The first devices were far less accurate than finger stick meters and were so painful that few people used them for long. But the information they provided mattered, for people with Type 1 could see, for the first time, the rise and fall of their glucose levels in response to food, insulin, exercise, and stress. This was a breakthrough.

New players entered the CGM market, bringing dramatically improved products with better accuracy and improved comfort. More people began using the tools, and lives were transformed. Notably, for the first time since the discovery of insulin, people with diabetes could be alerted to an impending low blood sugar.

One story is telling. About 8 years ago I had dropped my wife at the airport around 7:00 a.m. While driving home I received a text from Marissa: "Dad, don't panic." I pulled over, panicking. I read the rest of the message. "My blood sugar is 35. If you don't hear from me in 5 minutes, please call." I was a mile from the Cincinnati airport, and Marissa was in Tampa. Her boyfriend, Adam, was at work at Tampa General; his cell phone didn't work inside. I thought, what is 911 in Tampa? Can the first responders get to her before she passes out? I called, she answered. Her CGM had alerted her to rapidly dropping blood sugar, and she'd already treated it. Thirty-five was the low. She sat, I sat; we talked while her blood sugar rose. Her CGM saved her.

Today you are being asked to approve a new kind of CGM. The products on the market today are already wonderful. Yet Eversense brings an important innovation, implanted long-term wear. For some people with Type 1, today's devices are a struggle, elite swimmers, wrestlers, for example. Some people have sensitivity to the skin; others have body image issues. All would benefit from a CGM that is implanted. All deserve to hear their body's blood glucose symphony as it rises and falls throughout the day and be

warned before they need to reach out and say, "Dad, don't panic."

Thank you.

DR. BREMER: Thank you. Next is Dr. Dorothee Deiss from Berlin, Germany, and on deck is Josefin Palmen from Skurup, Sweden. Thank you.

DR. DEISS: My name is Dorothee Deiss, and my travel expenses are reimbursed by Senseonics.

I am a diabetologist from Berlin, Germany, with extensive experience in all CGM systems for 18 years. Since September 2016, I have been lucky to be able to provide the Eversense CGM system to my patients. Lucky, because a lot of them have had serious skin reactions or even allergies to adhesives of the other systems, which force them to stop wearing it. Up to now, no one showed any skin reactions to the Eversense adhesives, and some of them are using their seventh sensor.

I performed around 120 sensor insertions and 60 removals. It's a painless, uncomplicated, and quick procedure which I can integrate in my daily office routine. Most of the cuts are nearly invisible. Until now, I have not seen any severe complications, even not during several emergency MRIs. It is so much less a burden not to have to change the sensor every 1 or 2 weeks. For manually handicapped or blind people, the implanted sensor could be their only option. It's a true psychological relief not to have to think anymore about the risk to lose the sensor by changing the transmitter tape or accidentally pulling it off.

All of you know that there are still a lot of missed alarms with the current real-time CGM systems. The additional vibration alerts of the Eversense transmitter considerably increases safety, especially in situations where the patients can't look on the display or listen to alerts, for example, during sports, even during swimming, or young mothers holding their kids in their arms depend on vibration alerts.

My patients are very satisfied with the daily life accuracy of the sensor. In fact, those who used the Dexcom before estimate the Eversense system is still more accurate. Furthermore, there are no fake high posts by lying on the sensor at night like in other systems.

And one of my patients, who I know now for 18 years since their diabetes onset, has hypoglycemia unawareness with several severe hypoglycemic events. Unfortunately, she could not use the other CGM systems anymore because of skin reactions, and therefore she had to rely on the warnings of her hypo dog. She was so happy when she got the Eversense during a pilot study. Shortly after finishing the study and without Eversense, she had again a severe hypo with seizure, which even her dog did not notice. Believe me, it was her biggest present when she could go back on the Eversense right before her wedding and honeymoon.

Myself, I am wearing the Eversense system since more than 1 year. I can confirm the experiences of my patients, that the Eversense system is highly beneficial, effective, and safe to use, and I would even consider it in using it in my pediatric patients.

Thanks a lot.

DR. BREMER: Thank you. Next, we have Ms. Josefin Palmen from Skurup, Sweden, followed by Adam Brown from Arizona.

MS. PALMEN: My name is Josefin, and my travel has been reimbursed by Senseonics.

Lying, why are you lying to me? That was the first question I thought when the doctor told me I was diabetic at the age of 36. I was not big, I was not lazy. I was sporty. I can't be a diabetic, but it turned out that the doctor was wrong and -- was right and I was wrong. I had become diabetic, so I was in hospital for a week. After 3 days, I asked the doctor, "Can I go running, please?" The doctor looked at me and said, "It's good that you

want to do sports, Josefin, but isn't that a bit too early?" "Early?" I said. "I haven't been running for 4 days. I think it's rather late."

After 15 months, I called my doctor and said, "I need some help with my settings with my insulin because I'm going to do an Ironman," which is 3.8 km of swimming, 180 km of bike riding, and a marathon. And the doctor replied, "How much time do you got? How many weeks do you got to do that in?" I said, "Weeks? No, it should be done in a day."

Another race a few years later, I had very high blood sugar, so I wrote a report and posted it on Facebook just for advice. "I, if anyone, can appreciate and understand what you're dealing with because I am just like you. I'm Type 1 since the age of 3, and I'm also a long-distance runner," a man replied to me. That's one of the best words I've ever heard. "You should be on a pump," he said. So I used waterproof pump since I like to swim between Sweden and Denmark.

Of all the medical devices I've used, I think that the Eversense is the best. It makes me feel secure because it both vibrates on my arm and it beeps in my phone if something, if the blood sugar is going up and down. I used this since August 2016, so I'm on my seventh sensor. It's got predictable values, which is very useful when I do sports and in daily life. When I'm eating like this, I can see if it's dropping. And it's really good to have it for 6 months because it's actually under my skin instead of on me, because if I bump into a lamppost with other sensors, I can rip them off. This one is safely in there. It got the following function, and the main thing, it gives you so much higher quality of life because the Eversense has given me my life back because I knew exactly what life was like before the 24th of May 2010 and now I've got my life back. I can do what I want to. I dare to take insulin so I can perform when I do sports or if I'm at rest.

So thank you for this opportunity and actually to have my life back. Thank you.

DR. BREMER: Thank you. Next, Mr. Adam Brown from Mesa, Arizona, followed by

Dr. Timothy Bailey from Escondido, California.

MR. BROWN: Do the slides pull up or no? There you go. Awesome.

Well, thank you for having me. My name is Adam, and I'm a senior editor at diaTribe, and I lead diabetes technology at Close Concerns. I've lived with Type 1 since 2001 and have worn CGM for over 60,000 hours. My travel is paid for by Close Concerns. Over 16 nonprofit and for-profit organizations subscribe to Close Concerns, including today's Sponsor and every other major CGM company.

I want to make a case today for more CGM options, and I think, when we look at this slide, we should think this is a travesty. This is the most important technology since the discovery of insulin in diabetes, and three-quarters of people with Type 1 diabetes do not use it in the U.S. And these are at the very best centers in the United States in the T1D Exchange, over 20,000 patient registry. So when we talk about the average center in the U.S., when we talk about people with Type 2 diabetes on insulin, I think we should be really concerned about where CGM penetration is at now. And yes, it's rising, but this is why we need more options, and we need a wider toolbox to choose from.

And when you actually look at data about how much finger stick data do people with diabetes get, it's grim. People, on average, take two to four finger sticks per day, and those are insulin users who are titrating a dangerous medication every single day, self-titrating with different insulin sensitivities, and they have two to four data points to make a decision. So people not on CGM, I think, are in real danger right now with not getting real-time glucose information. And this is why this is important, because when people are diagnosed with diabetes, they're told it's just medication and food and exercise. There are 42 things that affect your blood sugar, and they interact in infinitely complicated ways that no person can manage and that no one can manage on two to four data points per day. So CGM is the single most important tool to manage this complexity in diabetes.

And when we talk about the approval today, this is such a no-brainer; this is a conservative application for an adjunctive labeling. The device is good enough for non-adjunctive labeling based on what the FDA has approved before. You've heard the foreign factor improvements that people love, the adhesive benefits. Let's think about expanding the CGM toolbox because we just need so many more options on the market because of how little data people are getting right now. And as someone that's benefited tremendously from CGM, I just feel like I'm on a mission to make sure that people have access to these devices. So when you're voting today, remember, remember this complexity that people with diabetes are facing and also just think about how many more people we could expand the toolbox to with a much better technology that's pursuing a very conservative label. Thank you.

DR. BREMER: Thank you. Next is Dr. Timothy Bailey from California, followed by Ms. Julia Neese from Munich, Germany.

DR. BAILEY: Thank you, Dr. Bremer and panelists. My name is Timothy Bailey. I'm speaking independently on behalf of my patients. I've not been compensated for my time today, but my travel expenses have been covered by Senseonics.

I'm an endocrinologist with 30 years of experience caring for people with both Type 1 and Type 2 and have extensive experience with continuous glucose monitoring, both in practice and in clinical trials. I became familiar with the Eversense CGM as an investigator in two clinical trials with the device and currently have just about as much or more experience inserting, removing, and observing the use of the device than any other United States endocrinologist. Meaningful monitoring of blood glucose levels, that is, the ability to both appreciate glycemic trends and to make correct decisions that lead to more stable and more normal glucose levels, changes lives. Meaningful monitoring is as critical to care as the choice of diabetes medications, in my judgment. The association between

higher frequency of glucose monitoring and lower A1c is well known. The data of our CGM trial confirm that hypoglycemia can also be mitigated by CGM. That, I learned much earlier from one of my patients who suffered from frequent hypoglycemia. At a clinic visit after he began using the first 3-day real-time CGM, he said that he was okay with using it, but his wife burst out, "It changed my life." Although CGM devices have now been available in the U.S. for more than a decade, as you've heard from so many others, not everybody who could benefit from this technology chooses to use them or can use them. Worse, nearly one-quarter of patients that start CGM stop using it within a year, compared to only about 3% that discontinue using a pump.

While cost continues to be a barrier, my patients stop CGM due to sensor adhesion problems, intrusive alerts, limited body real estate, and the need for repeat insertions. Now, remember, I'm an endocrinologist with no surgical training, so I thought it might be difficult to get patients to sign up for a study where the device had to be inserted and then removed by a second incision after just 90 days of wear. But to recruit 26 subjects for two studies took just 3 weeks, and to me, this validates patients' perceptions of the unmet need for new CGMs. We enrolled not just people with Type 1 using MDI or pumps, but also with Type 2 not taking insulin, and many had not ever even worn a CGM.

In addition to patients appreciating the system's accuracy, they found the Eversense device easy to use, comfortable, and very useful. Not having to insert and remove the sensor every 1 to 2 weeks was very important to those previously using other CGMs. The on-body vibratory alerts were an additional favorite feature. Sensor removal time by this non-surgeon was less than 5 minutes, and the procedure produced little discomfort. Overall, I am very impressed by the accuracy and ease of use this device. Approval of the Eversense device will favorably change the lives of the many people with diabetes whose needs are not currently being fully met by existing CGMs.

Thank you.

DR. BREMER: Thank you. Next, we'll hear from Ms. Julia Neese from Munich, Germany, followed by Maeve Serino from San Francisco, California.

MS. NEESE: Hello, my name is Julia Neese, and I'm from Munich, Germany. My travels were paid for by Senseonics.

I was diagnosed with diabetes Type 1 when I was 9 years old. I'm now 47. I started using continuous glucose monitoring more than 7 years ago, a really life-changing experience for me. And so far, I have used four different CGM systems, the Dexcom G4, G5, the Abbott Libre, and Eversense.

I have used three Eversense sensors in a row, and this is what I experienced: It's really easy, nearly pain-free insertion and removal process, and the little wounds heal really quickly. I have no skin irritation from the adhesives, even after 3 months wear on the same spot. I have accurate readings or I had accurate readings already about 2 to 3 days after insertion and over the full lifetime of the sensor and reliably warned of the low and high values, both through vibration of the transmitter on the skin as well as alerts on my devices. And Eversense was really the first system I was able to use with my smartphone and watch, which tremendously increased my attention and helped me take corrective actions whenever it was needed.

I experienced no transmission failures with Eversense and no compression lows like I have sometimes with other sensors. There are also no longer times with missing or unreliable data, no repeat warm-up times like with other sensors when freshly inserted or restarted, and there's no bumpy data at the end of the sensor lifetime. This has become even more important to me since last year, when I started using a self-made automated insulin delivery system. I can't use Eversense with it yet because there still needs to be some software written to integrate the Eversense data into my DIY closed loop system. But

I strongly believe that the just described singular features and benefits of Eversense, its accurate values, reliability, and uninterrupted continuity, make it perfectly suited for any closed loop system. And I'm more than happy to include it very soon.

Thank you.

DR. BREMER: Thank you very much. Next, we'll hear from Maeve Serino from San Francisco, California, followed by Dr. Daniel Finan from New York, New York.

MS. SERINO: My name is Maeve Serino, and I work for Close Concerns, a healthcare information company focusing on diabetes and based in San Francisco. Our work is supported by over 60 nonprofit and for-profit organizations, including today's Sponsor.

CGM is an incredibly valuable technology for people with diabetes, providing vastly deeper insight into daily glucose trends and patterns than SMBG alone. In many cases, this information can be lifesaving, and yet, CGM penetration in the U.S. is frustratingly very low.

This is data from the dQ&A Panel in over 1,500 people with Type 1 diabetes and over 1,600 people with Type 2 diabetes on insulin. If we rewind to 5 years ago and index the number of CGM users to 100 and then look forward to the most recent data from 2017, the panel has seen 36% growth in CGM in Type 1 diabetes and 20 to 25% growth in Type 2 diabetes on insulin. It's growing steadily, but for a transformative technology, it's not an exponential curve, at least in these users who are fairly engaged. The other main takeaway is to compare the trajectories of the two lines, and it's clear that the Type 2's on insulin are adopting CGM at a lower rate even though they can benefit just as much.

So how can we change this? By providing patients with more options, and that's where Senseonics comes in by (1) reducing the frequency of sensor insertions, only one every 90 days; (2) eliminating the receiver as a required device -- we all carry our smartphones; and (3) reducing common frustrations surrounding adhesives and site irritation. Late last year Senseonics reported approximately 25% of its users were new to

CGM, helping to expand the field in Europe, and we expect this number to further improve with future products that have longer indications and less calibrations. And not only is Senseonics attracting new users, Eversense is keeping them engaged and interested in CGM. Amongst existing Eversense users in the EU, only 9% have discontinued, half of whom did so due to reimbursement issues. There's huge potential here for Eversense to meaningfully increase CGM penetration, especially as more Type 2 patients move to insulin-intensive regimens. I strongly urge the Panel to vote in favor of Eversense, as it will expand the CGM category with a new form factor for patients.

Thank you.

DR. BREMER: Thank you. Next, we'll hear from Dr. Daniel Finan from New York, New York, followed by Lisa Laird from Merion, Pennsylvania.

DR. FINAN: Good afternoon. I am Dan Finan, a Ph.D. scientist who serves as Research Director at JDRF. JDRF is the leading charitable organization funding Type 1 diabetes research with a mission to accelerate life-changing breakthroughs to cure, prevent, and treat Type 1 diabetes. JDRF was founded by parents of children with Type 1 diabetes and is led by a board of people with personal connections to the disease.

Regarding financial disclosure, in 2002 JDRF funded some early stage research at Sensors for Medicine and Science, Incorporated, the previous name of Senseonics, and the grant terms included the potential for the company to someday pay funds back so JDRF can fund other research.

As you know, today, patients with Type 1 diabetes utilize a variety of medical devices to monitor and control their blood glucose levels. Self-monitoring blood glucose monitors allow patients to determine their blood glucose level through a finger stick. Insulin pumps allow for a continuous basal infusion of insulin to be given in addition to larger bolus doses at meal time. CGMs continuously measure the amount of glucose in the interstitial fluid,

and most recently available to people with Type 1 diabetes, artificial pancreas device systems, which consist of an insulin pump, a CGM, an algorithm, and a glucose meter, can automatically adjust delivery of basal insulin based on the CGM sensor glucose values.

We know, through a body of scientific evidence, that people with Type 1 diabetes have better outcomes when using CGMs. JDRF independently funded a landmark trial to evaluate the efficacy of adding CGM to intensive insulin therapy and found significant improvements in all measures of glycemic control without increasing hypoglycemia. Another study published in 2015 found that after 1 year of CGM use, almost daily CGM users experienced an 86% reduction in the number of events requiring emergency medical treatment compared to the year prior when not using CGM. And a 2017 study found that individuals using CGM lowered their HbA1c by 0.9%.

But despite these data demonstrating the benefits of CGM use, by most accounts, rates of CGM use in the U.S. among people with Type 1 diabetes are very low. This contributes to a state of diabetes care that leaves much room for improvement. Less than one-third of adults and only one-fifth of children in the United States meet recommended glycemic targets as measured by HbA1c. Rates of severe hypoglycemia and DK are unacceptably high.

JDRF believes that the availability of more innovative, safe, and effective tools is necessary to address the high unmet need in Type 1 diabetes. This includes additional types of devices such as CGMs with novel features and advances in performance, usability, accuracy, form factor, and safety that further mitigate the burden of Type 1 diabetes and improve quality of life. JDRF is supportive of people with Type 1 diabetes having more choices available for the tools they use in their daily lives, like CGMs.

Thank you.

DR. BREMER: Thank you. Next, we'll hear from Lisa Laird from Merion,

Pennsylvania, followed by Dr. Danielle Shapiro from Washington, D.C.

MS. LAIRD: Hi, my name is Lisa Laird. I'm a registered nurse and a certified diabetes educator of 24 years. I applied to represent my own view. Since then, the American Association of Diabetes Educators, for whom I'm a volunteer and I sit on the national advocacy committee, asked me to read their letter in addition to my own opinion. I have no financial disclosures. AADE did offer to pay for my travel expenses here today.

I do have two disclosures. Two of our four children have Type 1 diabetes, and we've been living with this as a family for 17 years.

My day job, I'm an inpatient diabetes care coordinator of a 300-bed teaching hospital just outside Philadelphia. Daily I see patients in DKA, elevated white blood cell count, and profound dehydration. Please communicate restrictions in the use of the Eversense CGM completely in these extreme patient settings. The same communication needs to occur for the use in CT scan, MRI, radiological procedures, including interventional radiology. I am reassured by the anecdotal evidence presented today of the misadventures regarding the MRI. I am convinced this will be safe.

In living with diabetes, differentiating trends in glucose with sensor technology is elusive. Even the most prepared individual is surprised by these excursions. It's imperative that this at-risk population of patients with diabetes have access to continuous glucose monitoring systems to prevent severe extremes in blood glucose, which can cause immediate and long-term life-threatening consequences. I agree with a positive review for the Eversense CGM system.

From Donna Ryan, the president of AADE, she's writing on behalf of the more than 14,000 members of the American Association of Diabetes Educators, healthcare professionals from various disciplines who provide care and self-management, education to people with diabetes and their caregivers; many of our members are providing training on

diabetes devices, including those used for CGM. She's writing in regard to this meeting.

"The management of diabetes continues to be an ongoing challenge for people with diabetes. Successful self-management requires continuous attention to proper nutrition, physical activity, medication management, and problem solving. Of most interest to your evaluation in the Eversense CGM system is the ability of a person with diabetes to self-manage all of these while self-monitoring their blood glucose levels and keeping them within optimal range. AADE believes that it is proven safe and effective. The addition of the Eversense CGM system for tools for people with diabetes to have available to them would greatly assist in the adoption of CGM."

She goes on to explain about the self-insertion and then the skin sensitivity being eliminated with the use of the Eversense.

"Statistics show that only a small minority of people with insulin-requiring diabetes choose to or afford the opportunity to wear and benefit from the CGM. I encourage the members of the FDA Advisory Panel to give a positive review for the Eversense CGM system. On behalf of the AADE, we would like to thank the FDA for consideration."

Thank you.

DR. BREMER: Thank you. Next, we'll hear from Dr. Danielle Shapiro from Washington, D.C., followed by Mr. Thomas Morris from Alexandria, Virginia.

DR. SHAPIRO: Thank you for the opportunity to speak today. I am Dr. Danielle Shapiro. I am a physician and senior fellow at the National Center for Health Research. Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policymakers. Those are the perspectives I bring today. We do not accept funding from device companies, and therefore, I have no conflicts of interest.

Patients with insulin-dependent diabetes need better options to monitor their

glucose. Ideally, this information can be used to make decisions about therapy and disease management. The markets for CGMs are growing. Although the Eversense device has more longevity and unique design features compared to those on the market, the Sponsor has not yet provided sufficient data to demonstrate the proposed benefits outweigh potential risks. We have several concerns.

Number one, we are concerned about the device's unclear benefits. Exactly what are the benefits, since the indication is in addition to rather than instead of self-monitoring blood glucose (SMBG)? Would any patients or providers want this device if they understood that (1) the device requires minor surgery; (2) patients may require more extensive procedures to remove the device; and (3) patients should not rely on the readings solely to make insulin dosing adjustments?

Number two, we are concerned that the changes made to the device hardware and software have not been tested in real time on actual patients. Of particular note, the new algorithm that was developed on the European dataset and tested on the U.S. dataset, post hoc, was not validated in real time. Compared to real-time clinical testing, post hoc data processing does not provide sufficient evidence that the device accurately measures blood glucose. Therefore, it can't be considered to provide absolutely valid readings. For those reasons, the Sponsor has not yet provided data that this device would be beneficial for real-world patients.

Number three, in addition to concerns about accuracy, we are concerned about potential risks during implantation and removal. We do commend the Sponsor for recognizing potential device failures and procedural complications. However, the Sponsor has not yet demonstrated that these post-trial design modifications would reduce or eliminate risks. It is reassuring that most providers were able to use these new instruments in the simulated scenario, but this does not provide sufficient data that this device will be

safe and effective when implanted with these new tools.

At this point, there is no urgent need for this device, so we don't want to rush on approval. Even if it is safe and effective, the Sponsor has not yet proven that it is safe and effective in the trial data. We urge you to recommend that clinical data be provided before the FDA makes a decision about whether to approve it.

In conclusion, patients with insulin-dependent diabetes do need better solutions to monitor and manage their disease. There is currently no full proof that the benefits of Eversense do outweigh the risks. We need additional clinical evidence before the FDA decides whether or not to approve it.

Thank you so much for the opportunity to share our perspective.

DR. BREMER: And thank you. Next, we'll hear from Mr. Thomas Morris from Alexandria, Virginia, followed by Dr. Sethu Reddy from Jacksonville, Florida.

MR. MORRIS: My name is Thomas Morris. I have never had any financial interest in the company or its product, and I came here of my own accord today, taking a day off from work and paying my own expenses.

I have been a juvenile diabetic for 49 years since age 10. I have been very fortunate. I had a world-class endocrinologist as a child. I have generally maintained good blood sugars and management, although as I get older, it's harder as the body becomes less sensitive to changes in blood sugar, and quite frankly, some diabetics' bodies are just more resistant to the disease than others.

I have been part of developmental efforts in the past. As a 14-year-old, I was a test subject for synthetic insulin. I was an early user of a glucose meter at the time in the early '70s. It was life changing. I had six blackouts prior to getting the meter. I have not had a blackout since I was a junior in high school.

The reason I came is that I believe Eversense can be a major step forward in the

management of diabetes for two primary reasons. The device allows immediate information on blood sugar readings -- too low, too high, trends -- and will assist in diabetics staying in appropriate ranges longer, a key to reducing long-term harmful aspects of the disease, and also will notify patients of immediate changes, which can be dangerous.

The other great benefit is many fewer finger pricks per reading. I have taken approximately 30,000 insulin injections. It is like brushing my teeth. The finger pricking is different. I don't know a single diabetic that doesn't, to some degree, detest the number of finger pricks required for good monitoring. Eversense, instead of one prick for one reading, will provide many readings for relatively few pricks of your hands. This product will lead to more usage and many more readings and better management. So I believe the product will continue to improve and ultimately rank with metformin and glucose meters and laser treatments for retinopathy as one of the major improvements in the last 50 years for diabetic management. I urge your approval for the product, which I believe will make many diabetics' lives healthier and better.

And since I have a few more seconds, I'd like to note that originally I was scheduled to go to a retirement party today, and I went to see the person that I'd worked with for 32 years and told him I was coming here instead, and I expected he'd be a little sad. What he did is he told me that his older sister died at the age of 40 from not having proper management of diabetes and urged that I come. So I would urge that you approve this product, and I thank you all very much for your time.

DR. BREMER: Thank you. Next, we'll hear from Dr. Sethu Reddy from Jacksonville, Florida, followed by Dr. Edward Damiano from Boston, Massachusetts.

DR. REDDY: Thank you. Good afternoon, my name is Dr. Sethu Reddy, Chair of Medicine at CMU College of Medicine, Michigan, and a member of the board of directors of the American Association of Clinical Endocrinologists and a member of the AACE Diabetes

Scientific Committee.

AACE is the largest organization of clinical endocrinologists in the world and plays a lead role in the care of those with diabetes. AACE supports the utility of longer duration glucose sensing technology that will increase the quality of life and safety for our patients.

Self-confessed, I've been an endocrinologist for 33 years, and I have guessed at diabetes management for most of that time period. I have no financial conflicts related to this particular issue.

AACE clinical practice guidelines recommend incorporation of CGM technology for nearly all individuals with Type 1 diabetes and many intensively treated Type 2 diabetes as well. The holy grail for diabetes management has been to normalize glycemic levels while avoiding hypoglycemia. Access to reliable, accurate, frequent glucose levels for as many days as possible will allow development of better treatment regimens.

Beyond the well-known complications of severe hypoglycemia, a recent analysis of severe hypoglycemia in older adults in the ARIC study has shown a significant association with cardiovascular disease and death, with a hazard ratio of 1.61. In 2017 the AACE consensus conference concluded that CGM is helpful to both children and adults with Type 1 diabetes and likely to benefit individuals with insulin-requiring Type 2 diabetes and those with diabetes in pregnancy.

Now, those with brittle diabetes must often check their capillary glucoses, as you've heard many times, 6 to 10 times per day, which result in a cost of approximately 2- to 400 dollars per month. CGM use can reduce the healthcare costs due to chronic diabetes complications, although more studies of the cost effectiveness of long-term CGM are needed. Imagine conducting the DCCT and ACCORD studies with incorporation of CGM technology.

I tell my patients that whenever they eat or play, they are doing an experiment. Our

clinical decision making is based on our summative impressions of those experiences. Our lives are made up of countless combinations of variables, and rather than educated guesses, which I have practiced, CGM will allow us to make evidence-based, data-driven, proactive care. Imagine driving at night with the headlights on every couple of hours. That is reality for many of those with diabetes today. I'm sure we will all agree that it would be safer and judicious to drive at night with the headlights turned on always.

Some of the barriers to use of CGM, while overcome by the proposed technology, are dislike for visible hardware, changing the sensor every 3 to 10 days, and the challenge of two pieces of external hardware needed for a closed loop system.

AACE believes that more options of CGM technology in a patient-centric world will allow us a personalized approach to diabetes management. On behalf of AACE, thank you for this ability to comment. Thank you.

DR. BREMER: Thank you very much. Next, we will hear from Dr. Edward Damiano from Boston, Massachusetts, followed by Mr. John Pettengill from New York, New York.

DR. DAMIANO: I want to thank the Committee for this opportunity. We have active collaborations with various sensor manufacturers, including Senseonics. I'm a Professor of Biomedical Engineering at Boston University and the President and CEO of Beta Bionics, a Massachusetts public benefit corporation that is directing all of its resources in the development of bionic pancreas for automated diabetes management.

I'm also a father, a father of an 18-year-old son with Type 1 diabetes. My son David developed Type 1 diabetes in infancy, nearly 18 years ago. He went on his first insulin pump, a MiniMed 508 pump, when he was 13 months old. Since then, he's used an Animas pump, the Abbott Navigator CGM, the Dexcom G4 and G5 CGMs, and the Tandem t:slim pump.

I have personal appreciation and deep respect for the need for a healthy variety of

therapy choices for people with T1D. Perhaps the most significant innovation in diabetes therapy over the past 20 years, really since the advent of insulin analogues, has been the continuous glucose monitor. Before I speak about the amazing technology Senseonics has spearheaded with the Eversense CGM, I would like to say a few words about my experience with continuous glucose monitoring.

The CGM is an integral technology component in our bionic pancreas. The first CGM we found to be accurate enough for the bionic pancreas was the Abbott Navigator. Steven Russell's team collaborated with mine to use the Navigator with our bionic pancreas in several years in inpatient studies in the Massachusetts General Hospital Clinical Research Center. After Abbott discontinued the Navigator in the U.S. in 2012, we found ourselves in a very precarious situation with no CGM. But just as all that was unraveling, Dexcom came through with their G4 Platinum CGM. After 4 years of running our own clinical trials testing different manufacturers' CGM devices in head-to-head-to-head comparison studies, we finally had an alternative CGM that was as accurate as the Navigator. Our bionic pancreas development efforts would surely have stalled had it not been for the team at Dexcom and their G4 CGM. But it cannot stop there. Just as Dexcom filled the void left by Abbott 6 years ago, new CGM technologies, including those by Dexcom, Abbott, and Senseonics, are raising the bar higher and bringing more diversity of choice to people with diabetes.

With the recent approval of the G6 Dexcom as a first integrated CGM, it is clear that Dexcom is continuing to be a leader in this spirit of innovation. With Abbott's recent collaboration with Bigfoot Biomedical, it appears that Abbott, too, is getting back into continuous glucose monitoring with their amazing technology. Small though they may be, the team at Senseonics has pioneered a bold alternative CGM therapy with an altogether different sensing technology that would offer a long-term wear solution and unparalleled convenience for people with diabetes. This is a categorically different choice and one that

has been long overdue.

Thus far, no one sensor has been able to provide universal appeal and meet the needs of all people with diabetes. People are far too individualistic to make that a realistic aspiration for any sensor manufacturer, and as long as that remains the case, it is essential that, to the health and well-being of people with diabetes, that diversity be encouraged and nurtured. I cherish the power of choice and the immense value that a growing and ever more diverse medical technology ecosystem offers the T1D community in spurring innovation and stimulating competition and encouraging individuals and agencies to participate and contribute to this newly invigorated industry.

Thank you very much for your attention.

DR. BREMER: Thank you. Next, we'll hear from Mr. John Pettengill from New York, New York, followed by Dr. John Laban.

MR. PETTENGILL: Hi. My name is John Pettengill, and I was diagnosed with diabetes over a dozen years ago. This past year I participated in a 3-month trial for the Senseonics Eversense system. They paid for my travel from New York City but not for my time.

I know it's already been a long day, so I wanted to liven things up a bit by sharing some PHI. My last A1c was 7.1. Now, I wish it wasn't. I wish it was just a little bit lower or even a lot lower, but the worst part is I know exactly how to make it lower. Eat fewer carbs in a sitting, eat primarily complex carbs, dose 15 minutes before I eat. It's not rocket science. But for diabetics like me, that gap between knowing and doing can feel very large. It's hard to always do what you're supposed to, and that means that any little hurdle, no matter how small, can add up to have an effect on my numbers.

I wanted to share some of the hurdles I faced with existing CGMs and explain how Eversense makes a difference for me. First, with a traditional CGM, I have to set aside time each week to insert a sensor into my pincushion of a stomach. This is a pretty big hurdle to

jump over 52 weeks in a row. This means I take some weeks off, and this has a negative impact on my numbers. With Eversense, I pre-committed, right, the concept from behavioral economics. I pre-committed to using a CGM, and it's always waiting here. And this completely removes that weekly obligation to insert a new sensor, and this is huge, and this alone can have a big impact on diabetes.

Second, with a traditional CGM, my site may hurt when I roll over, or it may simply tear off if I forget where I placed it and take my shirt off too quick. With Eversense, my skin isn't broken, and there's no discomfort or worry if I roll over or tear my transmitter off; it's easy to put it back on. And then, finally, with a traditional CGM, the transmitter has to stay in place for a full week. This means my skin gets pretty red and angry -- I have very sensitive skin -- from the strong adhesives that they have to use to keep it in place. Meanwhile, Eversense uses a milder adhesive, and that does make a difference. It doesn't have to stay in place for a full week, and this saves my skin from a lot of abuse.

I know these hurdles sound trivial and small, but after facing these hurdles every day for a year and then 2 years, they began to feel taller and taller. To diabetics like me, these hurdles matter a lot, and while, as consumers, we have more choice than ever before in home goods, electronics, technology, we have drastically fewer options when it comes to our constant daily, hourly, minute-by-minute companion. I'm 214 right now. We don't have very many options, not yet, so please give diabetics like me access to the Eversense system; it will make a difference.

Thank you.

DR. BREMER: Thank you. Next, we'll hear from Dr. John Laban.

DR. LABAN: Good afternoon. My name is John Laban, and I'm a pharmacist of 20 years with over 20,000 hours of experience working in retail pharmacy, speaking with patients, many of whom have diabetes. I've not been compensated today. I'm here on my

own will, but if someone wants to compensate me for my travel, I'd appreciate it.

(Laughter.)

DR. LABAN: First and foremost, thank you for your service and what you do to safeguard the public and facilitate innovation, progress, competition, and choices for diabetes patients.

While today we focus a great deal on numbers, statistics, calculations, what I would like to do for a few moments is bring to front of mind what is equally important, and that is the humanistic and practical considerations and benefits of the Senseonics long-term system. First is the benefit of prevention: One of the greatest risks all of our parents and grandparents often faced, and this is the very common incidence of slip and fall. With that said, here's a real-world example and the reason I'm here. Unfortunately, about 8 months ago, my mother, a long-term sufferer of diabetes who always had trouble identifying lows and highs, died of a slip and fall due to a hypoglycemic event which now could've been prevented by the Senseonics alert during the night. Instead of getting up to go to the bathroom, she could've felt the vibration and had a glucose tablet.

The second is the reality of what really drives adherence and compliance. When I reflect on the thousands of patients I have counseled and spoken to in the past, I can say, with utmost confidence, that what really drives compliance and adherence is participation and engagement. Having the implantable sensor is a continuous reminder and motivator to check and get involved. You see Senseonics gives a sense of control, responsibility, and capability. That is what drives adherence. As humans, people are competitive and love challenges. With Eversense, I can imagine my mom calling me to say that she stayed within the bars or that I can look at her data through the information-sharing app that Senseonics has.

The third and final reality point that I would like to bring up is that unlike other

CGMs where the patient is allowed to insert yourself, I believe the engagement with the physician who now receives training is a far better reality than other CGMs. Frankly speaking, do it yourself is a good approach and method for Home Depot and Lowe's but not for diabetes.

In closing, by approving Senseonics, you will add a ways and means to help elderly individuals avoid slip and fall, increase adherence and compliance, add the physician into the mix, and give the patient more options.

Thank you.

DR. BREMER: Thank you. We now have completed all the speakers who have registered. That said, there's a big audience here, and I know a lot of people have traveled far to participate, and with the acceptance of the Panel, I would like to open up comments to the floor. I think we have time for four comments, if any individuals in the audience would like to make a comment. I would ask that you feel free to come to the podium and adhere to the 3-minute rule, and then I'll ask, for the record, if you would state your name and affiliation. So the floor is open to anyone in the audience that would like to address the Advisory Panel.

(No response.)

DR. BREMER: All right, then I'll get points for staying exactly on schedule. We are now at 2 o'clock, so I now have -- following my script, I will now pronounce that the Open Public Hearing is officially closed and thank you, all. We will now proceed, according to the program, I see the panel deliberations.

As a reminder, although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we do request that all persons who are asked to speak identify themselves each time, and that is, again, this is for the public record. It also helps the transcriptionist to identify the speakers

and accurately capture the comments.

So, at this time, I'm going to ask the Sponsor to be available and to please respond to any questions that were outstanding, and I'll open it up to our Panel members. If there are any questions for our Panel members that we want to extend to the Sponsor, now would be the appropriate time. Panel members, are there any questions that were not answered this morning or due to time we weren't able to ask this morning? And/or follow-up? You know, we also had -- thank you, Commander. There was a lot of discussion during the morning. If there is anything that warrants follow-up or clarification, now would be the appropriate time during this meeting.

(No response.)

DR. BREMER: Crystal clear, okay. I will now, I guess, moving on and offer the same, are there follow-up clarification or further questions to our FDA colleagues in the room following this morning's discussion? Anyone in the Panel have any follow-up questions or other questions for our FDA colleagues?

Dr. Grunberger.

DR. GRUNBERGER: Yeah, I have a quick question. We were presented with data on Day 1 performance and Day 30 and Day 3 ramping up of the accuracy of the device, and we saw some data on Day 7, and from the SMBG data, it still looked like it was an initial ramping up for a person, maybe 7 to 10 days. Will there be any consideration, have any special warning on the device, on the reading of the device during the initial 7 days as part of how useful the data are?

DR. LIAS: You know, if the Panel finds that there are certain risks that should be mitigated, the Panel could recommend labeling as mitigations.

DR. BREMER: Thank you, Dr. Lias.

Dr. Burr.

DR. BURR: Yeah, I have a question, but I'm going to go back to the Sponsor. I know that the device that you're proposing to use has -- at least it hasn't been reported to be used as yet, but I'm curious, since I come from a part of the world with many people with very elderly skin, if you used any selection criteria in your studies, if you used any selection criteria in your studies that would not accept people who had unusually thin or atrophic or fragile skin for implantation.

DR. BREMER: And if I could ask all speakers, including Sponsor and FDA, just for the record, if you would identify yourself, that would be awesome. Thank you.

DR. GOODNOW: Sure. Tim Goodnow, Senseonics.

We did not use any specific selection criteria to rule out folks for any skin criteria. We did specifically target more mature people, people of age, to try to bring as many as we can over 65 to get some experience with skin of the elderly, but we didn't specifically target it out in any frame of reference at all.

DR. BURR: So at this point, there isn't a -- I'll use the word category of skin that you guys would consider as a relatively poor candidate for implantation?

DR. GOODNOW: We've seen no experience of skin impact.

DR. BURR: Okay, thanks.

DR. BREMER: Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

I also have a question to the Sponsor. Do I remember correctly that the first day after insertion, the sensor is silent?

DR. GOODNOW: Yes. Again, Tim Goodnow, Senseonics.

Yes. For 24 hours, the device, it is silent, and then on what we call the Day 1, the device wakes up. There are actually four calibrations on Day 1 and then two calibrations per day for the remainder of the duration.

DR. LAKOS: Actually, that was my question. So what you call Day 1 is actually Day 2 from insertion, right? It's the Day 1 after --

DR. GOODNOW: Yeah, it's the 25th hour after insertion.

DR. LAKOS: Yeah. I just wanted to clarify, thank you.

DR. GOODNOW: Right, right.

DR. BREMER: Dr. Tung.

DR. TUNG: Yes, the user manual says that high doses of aspirin can cause a false lowering of the glucose meter. I guess that means that if the glucose, the real glucose is here, the reading will be lower, and yet, for every other anti-inflammatory and many other anti-inflammatories in the list, there is no interfering effect. What is different about aspirin?

DR. GOODNOW: It is a potential at much, much higher doses than anything that's actually ever been reported, there is the potential for some binding of the salicylic acid, but we actually were not able to test it to that level, and it is well beyond anything that was reported. So, just in case any particular therapy got beyond what's supported in the literature, that potential is there, but it was never observed.

DR. BREMER: Thank you. I'm now going to take the Chair's prerogative, and we're going to go around the entire Panel for an opportunity for any last questions either to the FDA or to the Sponsor.

Ms. McCollister-Slipp, do you have any further questions or clarifications?

MS. McCOLLISTER-SLIPP: I don't have any specific questions necessarily for the Sponsor about this particular trial, but just one question, and forgive me, Courtney, if this is not the right place to ask this. What, from the Agency's perspective, are the requirements for considering, you know, the presence or existence of things like microvascular complications or dehydration or those kinds of things?

I mean, I have no desire to create additional barriers for device manufacturers at all, but it's just interesting to me that, you know, for a population of people that are so susceptible to these kinds of things, that something uses interstitial fluid, you know, very subject to capillary changes and hydration levels, that that's not a requirement or at least something, a point of interest, even if it's not part of like, you know, a point of efficacy.

DR. LIAS: Sure. Courtney Lias, FDA.

So for any device, you know, if there's a lot of different types -- if there's a lot of that type of device that have come through FDA, often there come to be norms of the types of information that's looked at. In cases where you have a new type of technology, a different approach is the starting point, and that's where you basically take a risk assessment approach. You look at the design of the device, the science behind it, certain mechanisms, then you assess what types of information might be necessary.

I'll give an example that if a new type of device came in to FDA, the sponsor would have done studies based on their own assessment of the risks that need to be assessed and the performance that needs to be looked at. Sometimes FDA will say, well, what about, you know, X based on the science of the device, and the sponsor may have a response to that or they may go out and do some additional testing.

So in this case you would look at the science of the actual device itself, the studies that were done, the information we can leverage from other types of information from the literature or other studies or experience with similar devices to determine a set of data that might be adequate for approval. Certainly, if the Panel has any recommendations for aspects that they'd like to either ask about or wonder whether or not additional data should be generated, they may make that recommendation.

DR. BREMER: Ms. Petersen.

MS. PETERSEN: No additional questions, thank you.

DR. BREMER: Thank you. Dr. Lakos.

DR. LAKOS: I have no question, thank you.

DR. BREMER: Dr. Goldsmith.

DR. GOLDSMITH: No questions.

DR. BREMER: Too easy. Dr. Rendell.

DR. RENDELL: Having been personally surgically challenged in the past by insertion of other devices and particularly removal, I'd like to know more about the success of the new insertion device and have some real-world data as to how many adverse events may occur with a new device and whether it's any easier than the old device and more successful.

DR. GOODNOW: What I'd like to start is I'd like to first ask Dr. Russell to come and speak to the insertion procedure that he went through with the existing device. He has, as he noted, about 25 patients that he inserted and removed, and he can speak to the training, and then we can talk about what we have with the new device.

DR. RENDELL: It appears the new insertion device does control depth of insertion.

DR. GOODNOW: Correct. That is the design intent --

DR. RENDELL: Right, which would be --

DR. GOODNOW: -- depth and angle.

DR. RENDELL: That would be new and certainly a good thing.

DR. RUSSELL: Thanks. Steven Russell from Mass General Hospital.

As Tim said, I've done about 25 of these insertions, and the training was briefly described, but in essence, you get a chance to practice the whole process on this arm with a synthetic skin substitute, and the synthetic skin that they used actually felt very much like the skin when I eventually did the first insertion, so it was a very good practice method to really feel like what it was going to feel like. And so to the extent that the new insertion

method was tested, you know, physicians were asked to do the insertion with that, that synthetic skin. That, I think, is a very good indicator of how it would actually behave.

The other thing I'll say is that I talked to Dr. Kelley, as I was learning this, and they were in the process of developing this new insertion tool, and essentially, what it does is it makes it impossible to mess it up in a way that -- as long as you're doing it right, those insertion guides wouldn't really affect what you're doing, right? The only way it would affect what you're doing is if you dove too deeply with the --

DR. RENDELL: Correct.

DR. RUSSELL: -- insertion tool. And so the other thing is that the thing that you use to make the pocket, right now it has two little lines on it, and you're supposed to insert it up to the depth between those two little lines, and what they did with the new insertion tool is simply move the handle up to that point so that if we put it back up there, they simply moved the plastic up to the point of that distal line. So, in other words, now it's impossible to insert it too far. But I guess my point is if you were doing everything correctly, you would have -- you'd do exactly what this new inserter would make it impossible to avoid doing, I guess is my point. So I haven't used the new tool, but I gave some feedback to Dr. Kelley when they were thinking about developing it. I think I'm confident that it would really improve the -- it would make the insertion process less vulnerable to inter-individual variation.

DR. RENDELL: Now, when you want to remove it, when I've had to remove similar devices, they've been larger, and you try to tip it up so you can get the head of the thing. How easy is the removal? And, in particular, with a tiny device like this, how easy is it to grab the head with your forceps?

DR. RUSSELL: Well, I found it pretty easy. Because it's fairly superficial, it's put in -- if it's put in appropriately, it's about 4 mm underneath the surface of the skin, so you can

very easily feel it, and you can kind of rock it between your fingers a little bit.

DR. RENDELL: Um-hum.

DR. RUSSELL: And so, in other words, if you push down one end of it, the other end pops up and you can feel it. And I always did the insertion or the incision to remove it at the exact same place that I'd done the insertion so I wasn't creating another scar, so you do have to reach, you know, a little bit to grab it, but because you can push it up with your hand, you can feel exactly where it was. So I would kind of push it up, feel it against my finger, and then just slide the tool in and then slip the forceps up so that they kind of went around it, which was easy to do. So I was pressing it down with my finger, taking the hemostat up like that until it slipped around it, then I would grab it and just pull it out, and it was really easy to do. And, again, you know, I'm not a procedure guy. I do entirely diabetes, so I wasn't even doing things like thyroid biopsies. It's been 15 years, but I found it pretty intuitive and pretty easy to do.

DR. RENDELL: How much bleeding?

DR. RUSSELL: Almost none. You know, you put in the lidocaine, you make the incision, and there would be a few drops of blood, I don't know, two or three drops of blood, and I would just hold pressure for a little while to allow it to --

DR. RENDELL: But now you're trying to remove it again.

DR. RUSSELL: Oh, the same thing. I would make the incision and just hold pressure for 30 seconds or something, that would be enough to stop the bleeding. And then I didn't usually provoke any additional bleeding by going in to pull the sensor out. So estimated blood loss, you know, was on the order of maybe a hundred microliters at most.

DR. RENDELL: Patient is on aspirin, patient is on Coumadin?

DR. RUSSELL: I can't say that I did any with patients on Coumadin, but I did ones with patients on aspirin and didn't experience any significant amounts of bleeding. And the

other thing which they didn't really talk about was that the closure is just with a Steri-Strip. So, I mean, you're not even suturing, and I would just hold pressure, you know, until I made sure that I was convinced that it would totally stop bleeding, you know; you let go and there's no ooze, and usually that's 30 seconds or a minute, something like that. And we didn't have any problems with bleeding later, after the closure with the Steri-Strip, so pretty straightforward.

Like I said, it was kind of fun to be able to do procedures again, and it's more fun, of course, when it's successful and it all goes well, and I actually wouldn't be surprised if physicians would find themselves enjoying doing these and looking forward to them, and I volunteered to do any that -- if anybody in my practice doesn't want to do them, I put my hand up.

DR. RENDELL: Okay, thank you.

DR. BREMER: Thank you. Dr. Gregg.

DR. GREGG: Sure. I had a comment and I guess a question. You know, overall the accuracy summary statistics appear that this device is comparable to prior, if not better, but it does seem that the one sort of soft spot that I kind of worry about is that -- I think of as false negative rate or what you referred to as a missed event detection rate or in other metrics where you're taking, for example, when the laboratory, the comparator, has a value in the 40s or 50s, this device is showing glucose in the 60s or above for maybe 30% of those cases.

And I'm kind of wondering, you know, if there are -- and recognizing, also, that the sample of low values in hypoglycemia may not be enough to really have a good picture of this, and I'm kind of wondering what, if there's -- I think of this actually as an adverse event because the reason why a lot of people are like this -- this is a great device -- is that it's seen as a safety net. But in that aspect of it, it's not perhaps always doing what it should, and I'm

curious as to whether there's sort of a focused intent to examine the accuracy at that part of the spectrum and then also perhaps what the postmarketing plan is for those areas for that.

DR. GOODNOW: Thank you. Tim Goodnow again.

If I could share some data in regards to the false positives, was the concern. Can we have the data? Yes. Let's see the concordancy table, if we could. And that was a specific question, the misses and 60 versus 70. So this is the specific results that you're referencing. So down the left-hand column is the reference of the true glucose value. The test device is shown in obviously the right-hand side of the table. Eighty-nine percent of the time the test device correlated exactly at 60 mg/dL or lower. There were a couple of occasions where it was 70 mg/dL, as you indicate, with all of them beneath certainly 90.

Can we see the low alert rate table performance overall? So there are some cases where it's off, I can show you representative tracings of what that actually looks like, but first let's look at the actual performance, alarm performance, with PRECISION. So this data, and again, if we're using -- in this case, we've highlighted 70. You can see 60 as well. The confirmed rate at 70 is 95%. We did miss five at 70 mg/dL with a true alert rate of 92 and a false alert rate of 8%. And Slide 27 here is the representative type of data, so when we see that we were off by 10 mg/dL, this is the type or error that we see. Obviously, we don't like being missed off at all, but these are not gross random errors; they tend to be generally systematic and generally do tend to follow the profiles, but there is a small error in some cases due to the physiological lag.

DR. GREGG: Yeah, I guess what I'm curious about, and maybe I want to make sure I'm not misinterpreting it, and that is that as I understand that, 11% of the time the value is truly under 60, you know, if you accept the comparator as a gold standard; in other words, it's 52 or whatever. Eleven percent of the time the alert will not alert that, so the person

would not have been alerted to that, so about 10%. Am I interpreting that right?

And I guess the follow-up question would be is in practice, does that mean, well, okay, a bit long -- a bit later, they would be alerted, but it's just a delay, you know, or are these -- or is this an issue of having sort of numbers around the threshold that are stealing that?

DR. GOODNOW: It is that balance of exactly how aggressive do you want to help your patient set the alarm? You could change it to 80 mg/dL. Could I have the table again, please? And, again, this is where some of the variable will come up. You know, to reduce the mis-detection, you could set it at 80, but at the expense, of course, is the false alarm rate. So that's the balance and tradeoff per an individual patient. You typically will detect it, but it is a matter of time, and it does have to do with the interstitial fluid, the translation to the capillary blood, and just how good is our algorithm in making that, making that transition. So you're exactly right, but that's the constant tradeoff that the patient and professional would make.

DR. BREMER: Dr. Grunberger.

DR. GRUNBERGER: Yes, thank you. George Grunberger.

Two simple questions: One, when you presented the results for the trials, there was an *n,* and I was just wondering how was that *n* of patients participating to U.S. data derived? Was that the discussion with the Agency, or who decided on the number of patients necessary to come to these conclusions?

DR. GOODNOW: Tim Goodnow again, Senseonics.

That is a conversation at the part of our IDE, so the investigational device exemption conversation and work that we do with the Agency to scope out the size of the trial and all the other parameters that we spoke of.

DR. GRUNBERGER: Okay. And the second question. As you know, the device is now

approved in Europe for 180 days from the -- so far from the experience from Europe, are there any new signals or anything coming up for people who wear it for 180 days versus 90 come up yet? Anything of concern.

DR. GOODNOW: Well, we really haven't -- the data that we do have is the people that are on the repeat insertion, so they are on their 91st to 180th day and 181 to 270. Can we have the safety data again? There really is very little -- there's nothing new. There's actually very little incremental safety data that's out on the third insertion as we know here, so this would be your third 90 day, so you'd be up to 270 days, whereas with the sensor you do see that we have two infections. Our largest adverse event rate is infections; it's at about 0.7%, 0.8%. And then the secondary procedure to remove the sensor. So that's why we have implemented the more robust training and cleaning procedures to really try to drive down that infection, and it's our proposal with additional training and the new tool that we do believe that we could reduce the depth and angle of the deep insertion, so that's the desire behind the change there.

DR. GRUNBERGER: And as far as performance beyond Day 90, any idea yet?

DR. GOODNOW: No. Performance, of course, we don't have the controlled in-clinic visit, but what we do have is -- could we look at -- so this is what we are able to do, if patients are willing to enroll and most frankly are, we have anonymized data that tells us how accurate is the device relative to the finger sticks that they do. So it's not as good as the laboratory analyzers, but what we show here is the 15/15 for first, second, third, fourth, fifth, sixth example, and obviously the numbers get pretty small through February, but you see there is a pretty consistent performance of 15/15 over the insertion cycles as well as the total duration of the sensor.

DR. GRUNBERGER: But these are repeated 90-day insertions?

DR. GOODNOW: These are repeated. I don't have data on the 180-day yet. Our first

patients to be inserted with those was November, December.

DR. GRUNBERGER: Okay, thank you.

DR. LIAS: Dr. Bremer, this is Courtney Lias.

I just want to remind the Panel, though, that we only have the 90-day claim in front of us right now.

DR. BREMER: Thank you. Dr. Tung.

DR. TUNG: I am curious as to how this device changes management. When you go from SMBG to this, do you end up giving more insulin, less? Is there a pattern, or everybody's different?

DR. GOODNOW: It's best suited -- I'll ask Dr. Russell to speak to that, who is experienced.

DR. RUSSELL: So this is Steven Russell.

This is a question I think about CGM in general as opposed to this device in particular, because I think that the way, in use, this is going to be very similar to other continuous glucose monitoring devices, and the claim that we have in front of us is a claim that it's as an adjunctive device, so tracking, trending, using the information. The things that I think you really see is the timing of blood glucose checks are changed; people know when to take a check. So, instead of just sort of taking it randomly, you can say, okay, it looks like I'm dropping low; I'm going to check and see if that's really true.

The other thing that's really helpful is knowing trends. So we teach our patients, when they have CGM data, instead of having a single blood glucose value of, say, 100 when you would calculate your -- or let's say 200, you'd calculate a correction dose, now we train them to base it just on -- not only on the blood glucose value but on the trend. So if you're 200 and flat, then you would calculate your correction dose one way, but if you're 200 and rocketing upwards, we might increase the dose by 20%. If you're 200 and dropping

dramatically, you might reduce the dose by 20 or even more percent from that.

And so what we see is that people get less variability in their blood glucose because they're able to pick their insulin dose more appropriately for the true circumstance, taking all that information into account, not just the static blood glucose measurement but that blood glucose measure plus the history and trend.

And then, in addition, having alarms is really, really important, and that's one of the things that I think is most helpful to patients, knowing that if the blood glucose is dropping, they're going to hear about that. Some of them choose to pick the alarms that look at the rate of descent, others pick thresholds, some pick both, but knowing that they're going to get an alarm and then they can check their blood glucose.

And then, finally, having the share options which again also other CGMs have, having, say, a parent -- that may not be relevant here because we have an adult indication, but let's say having a spouse being able to monitor you remotely, so not only would the patient get the alert but the spouse would also get the alert, and they could call them up and make sure, you know, honey, are you okay, I just saw that your blood glucose is dropping, do you have everything you need? When you combine all those things together, it just really creates a dramatically increased sense of safety, and we see better blood glucose control.

DR. BREMER: Thank you. Dr. Wyne.

DR. WYNE: I have just two questions, but related to what he was just saying, my understanding is that the NOW, which is the follow application, is not part of this package, correct? In other words, there's the application to receive the information, but for a family or friend to follow, that is not part of this application. So the mobile app is the actual primary receiver is part of the application?

DR. LIAS: Any software device that's a secondary display can be a separate type of

device that's exempt from FDA review.

DR. WYNE: Oh, really? Okay. Because he was talking about it, and I know it's available in Europe, but I didn't see it in any of these materials.

My questions have to do with there's just two things that they're related to. One is the description of the devices where there were problems with removal and others only a few, but I have a question related to that, and that's correlated back to the issue of what if someone comes into the hospital and maybe we don't know or they're not telling us or, you know, how we deal with hospital situations.

So, in most endocrinology offices now, we have ultrasound devices, and certainly, in the emergency room and in the ICU, we have portable ultrasound devices. The description of those adverse events, they used fluoroscopy to find the device and extract it. Could that have been done with ultrasound? And do you guys have pictures of what it looks like on ultrasound that maybe somehow that could be part of the training so people know what it's going to look like? And the corollary to that is if it can be found on fluoroscopy, then it probably could be seen on a plain x-ray, right? So if someone's in the ER and they get a chest x-ray and they see this in the arm, that would be one way to identify that it's there; is that correct?

DR. KELLEY: So Lynne Kelley.

So, yes, it is radiolucent, and so it is visible on x-ray. It's also visible on ultrasound. It's also visible by live ultrasound or fluoroscopy, and so all of those things are -- this is what it looks like on the ultrasound. You see the antenna and the shadowing below, and you're exactly right that in our training program, we've done two things. One is at initial training because, remember, we're training at first pass and they may not have been trained on removal, so we ask them to identify an individual surgeon or somebody who has done the procedure who's been trained on removal that would be their backup until they're fully

trained, so that's part of our training process. Or identify like a surgeon or something that they're friendly with in their clinic situation who would also be their backup.

Because it's right under the skin and easily palpable for a plastic surgeon, dermatologist, any of those people, it is literally a very simple procedure, and we have support staff 24/7. In addition, when you go to remove it, even if the sensor has outlasted it's time, so say it's past 90 plus 7 days and it's still in the arm but it's not transmitting glucose, the transmitter will still identify it, so you -- we teach to locate it using that transmitter to know exactly where it is in the arm so you're not lost.

DR. WYNE: But that has to be the transmitter that's linked to it. You couldn't just use any random transmitter?

DR. KELLEY: Correct.

DR. LIAS: Dr. Bremer, just one follow-up question to that. In the study that you had, our understanding is that three of the events, ultrasound was attempted; is that correct?

DR. KELLEY: So the ultrasound was actually used and it identified the sensor by ultrasound. The clinician was just unable to remove it even with the identification of location.

DR. LIAS: Thank you.

DR. BREMER: Thank you. Dr. Burr.

DR. BURR: Bob Burr.

This is a serious question for both the Agency and the Sponsor; it's not going to sound serious. Is there anybody who should not use this device?

DR. GOODNOW: Certainly, we are not seeking an indication at this point for pediatrics at all.

DR. BURR: I only deal with adults. If they're less than 18, they're non-issues.

DR. GOODNOW: You know, if I had --

(Laughter.)

DR. GOODNOW: If frankly -- if I had a 2-year-old child and he or she had diabetes, I'd put the Dexcom product in, in that child, right? This is meant for a point when they get to be a little bit older. So if I was in the position to do that, that's what I'd do. Other than that, we've been, you know, pretty successful with a pretty good variety of folks to try the products on.

DR. BURR: Okay, one specific class of people that I worry about, and that is people who are on chronic glucocorticoid therapy whose skin character changes quite a bit. I spend a lot of time taking out foreign bodies, so I get nervous about things resting under the skin for a period of time, so that's a category of people I'd be concerned about. Do you guys have any experience with that?

DR. GOODNOW: We have not, at this point, on any long-term corticosteroid therapy, so our best indication has been age at this point, where we've tried to see about 10% of the population at 65 or above.

DR. BURR: Understood.

DR. GOODNOW: The best we've been able to see is in the elderly population where we tried to get about 10% of the population at 65 or above.

DR. BURR: Okay, my population is about 40% 65 and above.

DR. GOODNOW: And getting closer to that, I'm more and more sensitive, yes.

(Laughter.)

DR. BURR: Okay, all right.

DR. LIAS: Dr. Goodnow, I have a clarification. Patients on glucocorticoid therapy were excluded from the studies, right?

DR. GOODNOW: That's correct. That's right, that's right. They were -- for our testing, that's right.

DR. KRAFT: Two quick questions: So the first would be default settings will drive probably a lot of what is actually used in practice, so I just want to make sure I understood correctly. Seventy is out of the box, the default setting for the low?

DR. GOODNOW: I believe. Can you confirm?

UNIDENTIFIED SPEAKER: Yes.

DR. KRAFT: Okay.

DR. GOODNOW: Seventy, yes.

DR. KRAFT: Okay, thank you. And the second would be, in looking at the adverse event profile, particularly around pain and irritation, I'm assuming these are all front-loaded with the procedural, so this is not post-procedural inflammatory reactions, pain, at the site?

DR. GOODNOW: I believe it's exclusively associated with the insertion and removal --

DR. KRAFT: Okay.

DR. GOODNOW: -- time period, right. Or possibly pain related to the IV access during the clinical trial, which not would exist with product use.

DR. KRAFT: Okay, thank you.

DR. BREMER: Dr. Lias, any further questions?

DR. LIAS: No.

DR. BREMER: To the Panel at large, any further questions, or has everyone felt they had an opportunity to discuss and inquire with the FDA and the Sponsor?

(No response.)

DR. BREMER: Seeing no hands, I will now declare a break, and I will go back to my script. Let's see. Let's see, yes, we will now take a 15-minute break. So, Panel members, please do not discuss the meeting topic amongst yourselves or with other members of the audience. I really do appreciate the insightful discussion. iPhone says it's 2:35. We will

resume at 2:50? We will resume at 2:50 p.m. Thank you.

(Off the record at 2:35 p.m.)

(On the record at 2:52 p.m.)

DR. BREMER: I want to be respectful of time and make sure those who need to leave tonight can get home at a reasonable hour while not shortchanging the important discussion. Okay. I will give Dr. Grunberger a few more seconds. As people are filing in, I want to once again thank everyone on the Panel and thank the audience and presenters, both the FDA and Sponsor, once again, for the insightful discussions and being accessible to answer and clarify questions as they came up during the previous hour. It's much appreciated.

Okay, so at this point now we're going to shift focus a little bit, and rather than there be a back-and-forth dialogue that we've had with the Sponsor and the FDA, this is more of a discussion amongst us as Panel members. I'd like us to really kind of focus our discussion amongst ourselves on the questions that the FDA has posed to us, both in written form in our packets as well as throughout the discussions in the presentation this morning. So, Panel members, the copies of the questions are in your folders, and again, what I envision for the next -- in the next hour or so is really a discourse and discussion amongst ourselves about the various questions that were posed. I would ask again, for the sake of the record and the transcriptionist, that you identify yourself before you speak. Even though I can see you, those who are reading the transcript won't know who's speaking unless we identify ourselves.

So, again, we have four major questions with various subparts that we'll kind of discourse now, and so, with that, I'll ask to show us Question 1. I'll go ahead and read the question just in case anyone can't see it, but then I will open the floor to our distinguished Panel to have that discussion. Well, I'm not going to read all of the subparts, okay, but I'm

going to read -- I'll read the overarching question.

So Question 1 -- this, again, was presented earlier, and we're circling back now. Due to the long wear period of this device -- again, it's being -- what they're asking, what's being asked for now is a 90-day approval -- the design of clinical studies is challenging.

And the FDA has asked us to weigh in on two following points, but we're not limited to the two points that are presented both on the packet and on the screen, and so I'll give 20 seconds to digest and read those, and I do, please, would love an open discourse amongst the Panel members. And just, operationally, what we'll do is we'll have the discussion, and I'll take notes and be the secretary up here, and as the discussion is winding down, what I will do is summarize to the Panel at least what I heard, just for clarifications, and then I'll report back to Dr. Lias about kind of where we stand as a Panel. So read away, and then please, please jump in.

(Pause.)

DR. GREGG: Are you ready for comments?

DR. BREMER: Yeah, we are ready for comments whenever.

DR. GREGG: All right, I'll share my comments. So I actually felt like the design was adequate to understand the different, you know, performance at different periods. I guess what I'm curious about is after the -- if a person, due to loss of insurance or loss of money or care, whatever, just keeps it on, does not return, you know, what happens after that point if some minority are basically extending the use? And I realize that's beyond the indication, of course, but I wonder if that should be included in an evaluation in some way, unless the unit just turns off. It does.

DR. WYNE: So what I understood from what the Sponsor provided is that at 97 days it turns off, but the only question I had there, is that 97 days from the first initiation, because as you read through it, there were certain events that can cause it to reinitiate

itself. So if you could reinitiate, would you extend the 97 days? And I had forgotten about that question until now, but the device itself is set up to go for 90 days plus a 7-day grace period, and then it just stops. That's what I read.

DR. BREMER: Dr. Lias, is it appropriate to ask any clarifying questions now, or are we kind of in a closed session?

DR. LIAS: You can ask, if you recognize them.

DR. BREMER: Yeah, I think that's --

DR. WYNE: So my specific question is I understand that it shuts off at 97 days. I also understand, from reading, that there are things that can cause it to redo its initiation phase. If it does that, does that reset the 97 days, or does it know that it's already at Day 14 of 97?

DR. GOODNOW: You cannot reset the day timer. The reinitiation referred to is just if someone were to not use it for a week, not do calibrations, it would force you into reinitialization of calibration, but you cannot change the 97 days.

DR. WYNE: So, at the end of 97 days, it shuts off --

DR. GOODNOW: Right.

DR. WYNE: -- and if the guy doesn't come back for a year, it's still going to be there but not doing anything?

DR. GOODNOW: Correct.

DR. WYNE: Yeah, that's what I thought.

DR. BREMER: Thank you.

DR. WYNE: I'll go ahead and comment. On the first thing, you know, my first thought was that when I first saw the data, my question was exactly the same as FDA, what's going on in the first 30 days, and I think that there is now quite a bit of data of what's going on in the first 30 days. And at first I was concerned about that data, but the application of the SW-602 really makes that data much improved, and I think that that new

algorithm is a great improvement, and I think it does give us sufficient information to know how it's going to behave and be able to use it over the full 90 days.

DR. GRUNBERGER: Yeah, I think along the same lines. Yes, I recognize that the 30-day gaps are concerning, but the performance doesn't seem to deteriorate beyond that. Whatever you see at 30 days doesn't seem to get any worse at 60 or 90, gives me a little more confidence that the data should be good. Again, the concern -- there's really only the first 30 days, and then after the SMBG data and the additional data, maybe the first 7 days. And, again, this was what I voiced before, and I just wonder how that's going to translate into whatever clinical guidance is going to actually be provided, what to do with the data if it's available the first 7 days.

DR. BREMER: Dr. Burr.

DR. BURR: Yeah, I had two thoughts. One is I think it may be important to know more about Days 1, 2, 3, 4 so that we can be more confident about which of those days the sensor reaches its mature performance so that appropriate caution can be used in the earlier days. The other one is toward the end of its current lifespan of 90 days, about 10-ish percent have failed by 90 days. It would be, I think -- and this might be possible to do based on data that's already been collected, would be to look at factors that influence its longevity. So, for example, in an individual whose sugars are higher than another individual, the sensing chemical may, in fact, deoxidize more quickly so that the sensor quits sooner. That has implications for the length of time between replacements. So if, for example, 10% of the sensors have failed by 90 days and the insurance company will pay for a 90-day replacement, then people are going to be going for 1 week or 2 weeks or 3 weeks without a sensor.

DR. WYNE: Yeah.

DR. BURR: And so I think that would be an important thing to understand before

people begin to figure out exactly how many sensors a year someone got and what the replacement interval ought to be. So that's my thought on that aspect.

DR. BREMER: Dr. Wyne.

DR. WYNE: So, you know, in terms of that first week, I totally understand what he's saying, but like I said with the application and new algorithm, that Day 1 is much better than it had been. The other thing is, from experience working with patients, even without me telling them, they come in and they tell me the first day is usually not very good, and so they're paying attention and watching for when it does become accurate. And so I think that, you know, within the patients who already use it, they're aware of it, and it's something that a patient who is paying attention to it is actually going to figure out quite quickly because that's what I've seen so far. So I don't know that we need to go back and have specific data for the first days in that first week. I think if Day 1 had stayed as poor as it was, it might be worth getting more data, but I think now we have, you know, pretty good numbers, and we know what patients realistically figure out on their own.

DR. BREMER: Please, Dr. Lakos.

DR. LAKOS: I think we also need to take into account intended use, so this device is not intended to make therapeutic decisions. So we already assume that it's not 100% accurate, so it needs to be confirmed by a home glucose monitoring system. So, from that point of view, I think that the accuracy in the first week is probably sufficient for the intended use, and I don't think it's significantly different from other approved devices.

DR. BURR: Well, just to introduce an air of reality, we know that they'll start to be used for therapeutic decisions within the first 2 weeks by most people, so regardless of what the fine print says, we know how they're used, so for what it's worth.

DR. GRUNBERGER: Okay, a general comment. It has nothing to do with this specific application. It's sort of interesting that we somehow think that the patients derive finger

stick readings are reliable and correct. And so, on one hand, I understand limitations in the system, but to think that what a patient is actually doing, a finger stick measurement, somehow is gold standard is just ridiculous, right? Between the cost of the strips -- you've seen the data by the Diabetes Technology Society -- the X parts, you know, strips, the technique, most patients are not using the second drop of blood. So certainly is funny we get so hung up on this accuracy and confirmation before clinical action is taken based on a finger stick, but the quality of finger stick data is probably not much better than what we see with CGM, I mean, as opposed to the YSI or the gold standard. But it's nothing specific with this one but, you know, when you demand a confirmation by finger stick, if someone assumes that a finger stick is going to be correct.

DR. BREMER: Dr. Tung.

DR. TUNG: If inflammation plays a role in the sensitivity of the monitor, then how it performs under conditions of systemic inflammation such as flu, cold, that kind of thing, would be useful information.

DR. BREMER: Dr. Lakos.

DR. LAKOS: Gabriella Lakos.

To the previous comment, I think we all know that the device may not be used exactly how it's described or prescribed, but at this point we are supposed to discuss the intended use, and we need to assume that it's used according to the intended use, and I think the Sponsor needs to put additional warnings to kind of draw attention to those areas where it's foreseeable misuse.

DR. BREMER: Thank you. And I also want to remind the Panel that we are in Part 2 of what was asked us, to consider the first question, was the issue of repeated insertions and whether there are potential concerns from this advisory body moving forward in that venue.

Dr. Kraft.

DR. KRAFT: So I would feel comfortable moving forward with multiple insertions with the data provided, so the first would be on an efficacy basis, again, for the package under consideration. Some of this is going to be extrapolated from actual use, but there's no evidence of a decrement in accuracy, so in terms of efficacy, that appears to be pretty good.

The second would be, in terms of side effect profile, it seems mostly additive and procedural and something that's not exponential. So the 6-month risk profile is probably pretty similar except for the fact that you're 6 months older than the previous 6 months.

And the third would be, with the exception of those of diminutive body size or, as Dr. Burr had pointed out, those potentially with skin thinning, the device itself is actually quite small, it doesn't take up a lot of real estate, so if we would think about pocket fibrosis, we just look at the size of the device and the size of the typical patient's arm, I would not envision an issue.

DR. BREMER: Dr. Wyne.

DR. WYNE: So I think I expressed my concern on that issue this morning, and while I understand what Dr. Kraft is saying, I'm still very concerned that one of my slender patients with Type 1 diabetes is, you know, recurrently inserting and removing from the same place over 10 to 20-plus years. What data do we do have that they can then inject insulin into that area? And I remain very concerned, specifically for my very slender patients, that this is going to take away area that they need to be able to inject insulin. And I say this because I have patients who have had diabetes for 40, 50, 60 years, and they're having problems with absorption and finding areas where they have reliable absorption of insulin, and now you're talking about taking away another area.

Now, if there was data to show me that it wouldn't affect the absorption of insulin,

I'd be very happy, but I don't feel having that data should prevent approval at this time; it just would be something I'd like to see once it's in use. The other group I'd like to see data on is my uremic and dialysis patients. But, again, that shouldn't prevent approval; it's just a group that needs to be studied.

DR. BREMER: Dr. Grunberger and Dr. Tung.

DR. GRUNBERGER: Yes. And I realize that, as it says that the current data don't include much experience with repeat sensor insertions, I was just wondering because we heard about alternating arm, so it's going to be left, right, left, right, and then so you give the arm a rest for 3 months. Is that going to be part of a requirement, or is there any experience at all with reinsertion in the same place? Do we know?

DR. WYNE: The current package -- Kitty Wyne.

The current package insert specifically says to alternate arms, so that's what it says, the draft we have.

DR. BREMER: Dr. Tung.

DR. TUNG: I guess I'd say that if you reframe that second question to say how many insertions are safe, we don't have the data to answer that question. This European patient registry finds 140 patients who have had it inserted three times. I don't know that that can tell us a lot about safety.

DR. GRUNBERGER: But we heard some were sixth or seventh already.

DR. TUNG: Yeah, there were 14 in this registry --

DR. GRUNBERGER: Yeah, yeah.

DR. BREMER: Dr. Burr.

DR. BURR: A question for the Sponsor: In people who are getting multiple insertions, alternating arms -- oh. I'm sorry, sorry. I just wasn't close enough. Relaxing here.

In people who are getting alternating insertions, so they're getting two insertions per arm per year, do you guys provide direction, parameters about how far apart the insertion site should be, assuming that they can identify the earlier one with a little small scar?

DR. GOODNOW: We haven't had a need to do that as of yet. The practice typically has been if they can find the scar, they'll use it, but typically after 90 days, it's hard to see.

DR. BURR: So they reinsert it in the same place?

DR. GOODNOW: They try to use the scar, yes.

DR. BURR: So, in effect, the sensor is really occupying this little, small cylinder tissue in the arm and doesn't really -- it's a very small surface area.

DR. GOODNOW: And, again, we don't have the controls that you'd have in a controlled study, of course, but what we do train and typically, for the aesthetics, if they can see the insertion point, which frankly is not common after 90 days, they will look to use that again.

DR. BURR: Okay. And we don't know if someone keeps getting it inserted in the same area 12 times or 14 times, whether that begins to change the efficacy?

DR. GOODNOW: We don't know yet. We haven't done that evaluation. We'd certainly be willing to anticipate that as part of the post-approval studies.

DR. BURR: Well, that's a far-forward looking thing.

DR. GOODNOW: Well, 12 and -- yeah. And we are moving to 180 days in Europe as well, so that changes the reinsertion dynamic there as well.

DR. BURR: Okay, thanks.

DR. BREMER: Any other comments from the Panel members?

(No response.)

DR. BREMER: I will summarize and present my quick summary to you guys in the

group, and then feel free to edit before I present it to Dr. Lias.

So what I'm hearing as far as the -- as far as in general, in scope, the data presented to us by the Sponsor and reviewed by the FDA does suggest, with the additional studies after the first ones with the 1 day, 30, and then -- I guess, 1 day, 30, 60, and 90, that there is sufficient data that this suggests that even in the initial week, if you will, then, that there's safety and efficacy data that's sufficient, with the caveat that in the first few days post-insertion there will be the opportunity for the user to kind of fine-tune their management based on their experience and the recognition and that there is a time period after the insertion of the device before a sensor reaches stability or a maturity, if you will, and that based on the current data and the data that's been presented to us as far as the repeat exposures or repeat insertions of the sensor, although there are questions about longevity and real estate and other aspects that are individual to each particular patient, the data presented to us seem to be sufficient with concerns or questions of others about how this system, even with the current 90-day request or 3-month request, may function in different patient phenotypes, whether dialysis patients, uremic patients, patients during periods of stress or an infection, or patients with other chronic conditions that were excluded from the enrollment criteria, the data, the trials and the data that were presented to us.

And other questions I think that were brought up, and concerns, would be the absorption of subcutaneously administered insulin in sites that were previously used for the Eversense insertions. I think there's no data presented, and I think that's a question that the Panel has come up -- both this morning and this afternoon. Does that adequately capture the discussion?

(No response.)

DR. BREMER: Did I omit or overstate anything?

(No response.)

DR. BREMER: So, Dr. Lias, is that sufficient to you and your team or useful as far as your question?

DR. LIAS: Yes, thank you.

DR. BREMER: You're quite welcome.

Okay, now I will ask on the screen and Panel members to please flip to Question Number 2. This one I will read because this is also very important, and it was brought up this morning in our discussions with the FDA.

So following the clinical assessment and the data that was presented to us before the meeting and during the presentations this morning, Senseonics has made four system design modifications. As a panel, we will discuss right now whether there are important considerations related to safety or effectiveness that should be considered for each of the following four modifications, and if so, please discuss the types of actions that we may give recommendations to the FDA to address these considerations. And, to recap, the four modifications that were made include the modified glucose determinations algorithm, which we discussed in the previous question and which has come up quite often today; the modified transmitter design; the modified sensor end cap design; and the modified blunt dissector tool.

So I open the floor to the Panel for any discussions regarding those four changes that were made after the trials.

DR. GRUNBERGER: Can I just make a comment?

DR. BREMER: Dr. Grunberger.

DR. GRUNBERGER: A comment I already sort of brought it up this morning is that basic scientists, obviously it makes me shudder because you change stuff in the middle of the trial, and then you ask for, you know, an approval based on educated guesses, in a way. But as a clinician I was pleased to see these changes (a) make sense, (b) seem to improve

the equation, and as long as there's enough postmarketing, very strict vigilance and surveillance, I don't think that this should affect the safety or the effectiveness of the system.

MS. McCOLLISTER-SLIPP: As a patient, none of this bothers me. I mean it's not like we're changing a drug; these are specific things that are happening from the algorithm, we understand. Now, algorithms work. We understand the data; there are ways of testing that. I mean, the other things seem to be improvements based on safety. So I would imagine that the Phase IV studies and future data is going to be looking for that, and the company is going to be looking pretty closely to see if there are any changes, you know, any issues that rise as a result of those changes. But I mean, personally, I think this is encouraging that we're not requiring the company to stick with the old design, that we're allowing them to make improvements to the design as they move through the process.

DR. BREMER: Dr. Wyne.

DR. WYNE: Actually, I would want to echo what Dr. Grunberger said because my feelings are exactly the same pattern as his. From a practical clinical point of view, what these are really is improvement in safety, and so, yes, you've substantially changed the cap, you've changed the dissector, but you're still using the same tool, you've made safety modifications, and so I think, from a clinical point of view, each of these four components make me feel safer to use the system.

DR. BREMER: Dr. Lakos.

DR. LAKOS: I wanted to add a comment regarding the algorithm. So, from industry perspective, actually, it's quite often used, the procedure. Nowadays, we use machine learning algorithms, so that's what we do; we change the algorithm, and we reprocess the data. So this is not unheard of. And I'm actually happy to hear that FDA is recognizing it, and that's why I asked the question has there been a precedent that actually these data

were used, and I'm happy to hear that it was. So, again, I can confirm that this is kind of standard practice nowadays in industry when it comes to algorithm and software development. And, obviously, there are plenty of safeguards about software verification -- when it comes to performance, this is a very frequent practice.

DR. BREMER: Thank you.

DR. WYNE: And with respect to what you were saying -- this is Kitty Wyne again -- remember, too, the CGM data that's used in, in silico modeling to look at the accuracy of the CGM. And so, for me, as I went through the data, I was actually expecting to see in silico, and here we are, we actually have a full database of patients, and so they were actually able to apply the new algorithm to the actual real-life patients wearing the device, and so, to me, that was actually reassuring, and to see that it actually improved the accuracy, of course, I was looking to make sure it did improve it, and it did.

DR. BREMER: Dr. Burr.

DR. BURR: Yeah, Bob Burr.

The only thing I would mention, I think the top three are fine. The one thing that would be good to determine as early as possible is whether or not there is a category of people for whom the insertion presents more than average risk. For most people it's a trivial consideration, not a problem, but I can't help but believe that there isn't going to be discovered a category of people for whom the method of dissection using the blunt dissector is going to lead to complications and issues: people with fragile skin, older people, people on glucocorticoids.

So I would encourage the Sponsor and perhaps the Agency to think about adding a component to the approval that for those people that the Sponsor has trained in the use of the dissector tool, that some kind of a registry be established so that for the first 1,000, first 2,000 insertions, there's actually data coming back about those that were fine and those

occasional ones that led to an issue, and perhaps there'd be an identifiable problem that could then be used to either modify the tool further or identify a category of people that the insertion should be done in a different way, perhaps instead of blunt dissection, more of an open technique. I think, as the use expands, which I think it will, it will be moving into people who perhaps this technique would not work well on, for what it's worth.

DR. WYNE: So are you suggesting a U.S. registry similar to the European registry?

DR. BURR: Yeah, yes. Although --

DR. LIAS: Courtney Lias.

We have a question on post-approval recommendations on Number 4. That would be a good place to weigh in on things that you would want in the postmarketing phase. Thank you.

DR. BREMER: From the Panel, any other comments or questions or input regarding Question Number 2? You're right, Question Number 4, I think there will be lots of more -- lots of comments, but regarding this question.

(No response.)

DR. BREMER: If not, I'll summarize, and I feel the consensus of the panelists suggest that there are no major concerns regarding the design modifications that were made after the studies and that were presented to us today and in our materials, with the caveat that there's also no real patient experience and so that, moving forward, kind of segueing into subsequent questions, that the real-world experience with these modifications be tracked and recorded by the Sponsor.

Dr. Lias, is that helpful to you and your team?

DR. LIAS: Yes, thank you.

DR. BREMER: Thank you. Okay, and we will now proceed to Question Number 3. So, Panel members, one question down on your sheet, and I'll read it to you here on the

screen.

Senseonics has identified three drugs that may interfere with sensor readings: tetracycline, mannitol, and sorbitol. Please, amongst ourselves, we'll discuss whether Senseonics' proposed labeling mitigations are adequate and sufficient for each drug interferent. All right, we'll open the floor.

Yes, Dr. Rendell.

DR. RENDELL: Clearly, we all use doxycycline and minocycline. We use it for acne, we use it for MRSA, so it would seem that we need information on whether or not the absorption spectra of minocycline and doxycycline are such that it would interfere with the sensor readings, and if so, then clearly the sensor would not be appropriate during treatment with doxycycline or minocycline either. It brings up a general question as to whether the FDA has information on absorption spectra of agents that come through the approval process. That's been a question that has intrigued me.

DR. LIAS: Courtney Lias.

We can always ask, but I would doubt that that would be typically the case. However, one of the things that would be helpful to know is whether -- if they find one. Sometimes sponsors may choose to assume interference rather than testing it and just label against it, so it would be helpful to know whether the Panel believes that labeling against use is adequate or not, and if there are suggestions about what the Sponsor has proposed as a mitigation for, for example, tetracycline.

DR. BREMER: I guess I will ask a question to the Sponsor, if there is any information regarding doxycycline and minocycline.

DR. GOODNOW: We have not yet tested doxycycline. What we do know, from the other fluorescent drugs, is the wavelength of interest for us is that 390 nm. So we had tested the other optically active compounds that are shown there, but in regards to the

other tetracyclines such as doxycycline -- can we put up 33, please? We have tested tetracycline; we have not tested the other, but given the molecular structure, which we can all enjoy, we fully anticipate these compounds to have the same optical characteristics and therefore absorb the 390 nm of light that would be of concern. So our suggestion, we can certainly test it, but my hypothesis would be, right away, they should perform the same.

DR. BREMER: And for clarification for the record, perform the same as what?

DR. GOODNOW: As the tetracycline, sorry. All of these are --

DR. BREMER: Thank you.

MS. McCOLLISTER-SLIPP: One question. Oh, sorry. Go ahead.

DR. BREMER: Yes.

MS. McCOLLISTER-SLIPP: So for the clinicians or anybody else on the Panel who knows this, I mean, if for tetracycline or minocycline or doxycycline, whatever, are there adequate and frequently used substitutes? I mean, I try not to take antibiotics unless I absolutely have to, but if I have to, I want them and I want them to work. So, I mean, I haven't taken any of those, that I'm aware of, for a very long time. I used to take tetracycline when I was younger, but I mean are there substitutes? Is this going to be an issue?

And I guess the other question is I'm sort of a nerd, and I would know what class of antibiotics I was on in most cases, but I don't think that's something that most people would be readily aware of, and from your perspective as clinicians, I was just wondering if you think that that's something that should be considered or what your sense of that might be.

DR. WYNE: So Kitty Wyne here.

Those are not our first go-to antibiotics for our most common infections. So, for example, in primary care, there's only a couple specific things you'd be using it for; there

are some specific things in the hospital you'd be using it for. But it's a reasonable precaution to tell a patient about it when they get this, just that they need to not trust it while they're taking one of those antibiotics of that class, and that is something that you can remember because there's also only a few precautions with it.

So I think it's reasonable to put it onto the label as a class recommendation, but my concern is we need a little bit more guidance other than avoid it because, again, patients are going to keep an eye on their finger stick and know when it starts to match up, but I need to be able to tell you, if you get doxycycline, minocycline, we really don't use tetracycline, you're going to have to not trust it for so many days, and we need a little bit of guidance there.

In terms of mannitol and sorbitol, that's really a procedural-related issue, mostly in the hospital but some outpatient procedures. So it is, again, just an educational issue. But we need to know how long after they receive it.

DR. BREMER: Please, Dr. Tung.

DR. TUNG: I guess I'll add that it's not inconceivable that a patient with the device shows up for surgery in which mannitol is commonly given. One is a kidney transplant, and the other one is cardiopulmonary bypass, both of which often have mannitol involved in how they go. So how long that effect lasts would be interesting but not part of this.

DR. BREMER: Dr. Grunberger.

DR. GRUNBERGER: No, just to help me out with this question, does FDA have a slide which we can actually see what is the Senseonics proposal, labeling mitigation so we can discuss it? Because maybe I just couldn't find it. I mean, I can see in the proposed package insert, contraindication mannitol, sorbitol; tetracycline's not mentioned. So do we know what labeling mitigations are?

DR. LIAS: Senseonics had a slide on this. Senseonics, can you pull up the labeling

recommendations you proposed?

DR. GRUNBERGER: Yeah, thank you.

DR. LIAS: Thank you.

DR. WYNE: And, actually, it's on the labeling but not the package insert, correct? Because I was just scanning through my package insert, I had highlighted it, and I think it's only -- it's on the -- not the patient labeling, but it's on the package insert piece.

DR. GOODNOW: At that point, that is draft labeling. We'll continue to work with the Agency so it will be everywhere it should be. If it's not in the draft, it will be.

DR. BREMER: Dr. Kraft.

DR. KRAFT: So I'm heartened that for tetracycline, this is a mechanistically based interaction, right, so this is well established, and presumably, there's a dose response here also. So these are knowable effects in terms of the latency. So, you know, a conservative would be five half-lives. You know, by three half-lives, 90% of the drug is gone. The interstitium will be pretty reflective of a central compartment also, so you know, again, I would probably advise for a class recommendation for the tetracycline, and then I think, again, three to five half-lives is reasonable. The sorbitol and mannitol also could be in a similar construct, understanding that both of those would be in situations, for the most part, that are not ambulatory monitoring using the device.

DR. GOODNOW: We certainly understand the value of the clearance -- when can I start to use my device again -- that certainly makes sense.

DR. BREMER: Dr. Lakos.

DR. LAKOS: One more comment regarding interferences. I don't know if any type of contrast material was considered that is used for imaging, x-ray, and CT. Currently, I know MRI and maybe even CT is contraindicated but x-ray is not, if I'm correct, so any type of contrast material that can interfere with the chemistry.

DR. BREMER: Dr. Lakos, is that a question that you want to pose to the Sponsor?

DR. LAKOS: Yeah, that's a question. Yes. Sorry.

DR. GOODNOW: Sorry, we have not tested it at this point but certainly have the ability to identify. Again, as you point out, there are two mechanisms: Does it bind to our indicator, which can be tested pretty quickly, and does it have an optical characteristic at 390 nm? So those are actually pretty easy to figure out with robust testing.

DR. BREMER: To the Panel members, any other comments regarding this question? And then I will summarize.

(No response.)

DR. BREMER: All right, seeing no lights, as far as the summary of this discussion, I think all of us, in general, do agree with identification and notification that the three drugs, the tetracycline, mannitol, and sorbitol, do need to be displayed, both at the positioning and patient, either in the -- both probably in the forms of package insert and product label.

As far as the concerns and questions that were raised for further interrogation, it could be to recommend to the FDA that rather than explicitly saying tetracycline, use tetracycline as a class name and also tetracycline derivatives or as a class of drug rather than a single agent in that particular class and recommend that a class effect be determined as far as interference. And also recommend some guidance from the Sponsor about clearance and legacy effect, if you will, of when the estimation of the sensor would be more accurate following the discontinuation of the interfering agents.

Is that a succinct summary, and did I miss anything?

(No response.)

DR. BREMER: Dr. Lias, is that helpful to you and your group?

DR. LIAS: Yes, thank you.

DR. BREMER: Wonderful. Okay, we will now go to Question Number 4, which we've

hit on before, but this is a question -- and, again, just like all questions, I would appreciate a lot of discussion. So I'll read it for you.

If the device were to be found to be safe and effective based on the existing data, Senseonics has proposed to conduct a post-approval study to gather additional information about their system. Amongst the panelists, please discuss the types of information, if any, that would be important to collect during such a study post-approval.

Dr. Kraft.

DR. KRAFT: So one piece of information I think that we don't have to collect is dexamethasone. So if you look at the assay, which was extremely sensitive, it is at least one order of magnitude more sensitive than the minimally active biological effect level, so MABEL level. And if we look at inhaled corticosteroids, this is probably our best drug comparator, it's probably at least two, and maybe more than that, orders of magnitude off any detectable -- HPA suppression is probably the first thing that you could measure. Other long-term effects of inhaled corticosteroids are even harder to do so.

So as somebody who runs clinical trials, I think it's important to focus on information and time and energy and measure on things that bring you information and not collect information that's non-informative. So I would advise against dexamethasone. I think that the issue with the data presented has essentially put the nail in the coffin about any concerns of dexamethasone.

DR. BREMER: Dr. Wyne.

DR. WYNE: Clinically, I agree with that, and the piece of data that was actually reassuring to me was that when they looked at the device at removal, 85% of the dexamethasone was still in the device. I think it would be of value to do that in this post-approval study just to confirm on a larger scale that it does stay stable at that 85%. But I agree that there is no reason to keep doing all the levels. And, you know, if you do the

math of how much is actually released and you look at what we give with inhaled, with Medrol Dosepaks, etc., it's actually pretty reassuring to know that 85% stays in the actual sensor.

DR. BREMER: Ms. Petersen.

MS. PETERSEN: Thank you. Carolyn Petersen.

So today we talked a lot about the device and about some risks, you know, of the various components of it, but I think we also have an opportunity to look at the patient experience as a whole, first taking into account that we have the patient reality that exists if we don't have a device like this and to think about what we can suggest, recommend, greatly recommend to FDA to help find the patients for whom the risks really are in appropriate proportion to the benefits that patients may obtain. So we can look at decision aids that help clinicians find the right patients who may truly benefit from this system, having the appropriate motivation and the ability and willingness to do the work necessary to get the benefits from it. We can look at the kinds of patient education that is necessary before insertion and the kinds of trainings that would be appropriate for the providers in the real-world settings, you know, in urban clinics, nurse practitioners, physician assistants, family physicians. I think we've seen we can achieve a pretty good level of success in academic medicine, but that's not where most patients with diabetes are treated. And you can go a great way in terms of ensuring success with this type of device by looking at some criteria in that area.

And, finally, I think this concept of a postmarket registry that allows retrospective analysis of patient characteristics of various positive and negative experiences will help identify the patients for whom the benefits really do outweigh the risks and also identify patients where there may be some risks we don't know about today where we should be thinking about some other kind of system in their decisions with their providers.

DR. BREMER: I've been ignoring Dr. Grunberger all day, so -- okay, thank you.

DR. GRUNBERGER: George Grunberger.

I agree, first of all, with everything Ms. Petersen said, and I think that clearly, in the postmarketing plan or surveillance, some things are obvious. I mean, you will look at the effectiveness, adverse events, hopefully some -- whatever safety signals. But, you know, FDA, as you know, is trying to move the whole beyond A1c in the diabetes management arena and beyond the time in range and the minimizing time in hypoglycemia; the third sort of area which is being looked at, which has been difficult, is the patient-reported outcomes, because it's nebulous, it's very subjective. And so I would urge the Sponsor and FDA to hopefully use whatever state-of-the-art patient-reported outcomes validated instruments exist, because that's been obviously tough to get, and hopefully, we can get to a stage where we can provide guidance to industry, which will actually use the patient-reported outcomes, which make sense for everybody.

One of the things which is missing usually is the clinician satisfaction scale, and so this is going to totally change, if approved, what endocrinologists are doing. You heard Dr. Bailey and Dr. Russell, they're happy interventionists now, and as we define a new era of interventional endocrinology, I think we have to also gather input from the clinician satisfaction scale.

Thank you.

MS. McCOLLISTER-SLIPP: Yeah, in terms of -- Anna McCollister-Slipp.

In terms of additional data for postmarketing -- I've mentioned it before, I mentioned it in previous CGM outcomes -- I think it would be really helpful to get more data on people who do have microvascular complications. You know, I would love for somebody to show me whether or not, you know, that is an issue. I haven't seen a definitive case one way or the other. Also, hydration level, I don't necessarily know how you could measure

that adequately. I know there are people who are working in different ways of doing it, but you know, as somebody who has kidney disease who takes diuretics for that who does have hydration fluctuations depending on the weather or what I ate for dinner last night or, you know, how I slept, that can be important, especially when you're dealing with interstitial fluid, which presumably could be impacted by hydration levels.

And then I also would like to concur with the suggestion that we do patient-reported outcomes of one form or another, and I don't think we need to get too onerous in terms of coming up with a whole bunch of requirements for a Phase IV study because I know that increases the burden, increases the issues related to powering and all that kind of stuff.

But given the fact that this is an app-based receiver that we'll all be doing, you know, done through an app, doing a postmarket registry would be relatively straightforward, and the ability to add in PROs through an app-based interface would be a relatively straightforward way of doing it, and you know, it would encourage coming up with ways for patients, whether it's through the app or through some other mechanism, to be able to report their own AEs without necessarily having to report it to their physician, because we don't. I mean, sometimes we do if we happen to be there right after it happens, but for the most part, it doesn't. But if you have a skin irritation or hyperpigmentation or something, if it's a relatively straightforward process for reporting that through an app, then that would be -- we would get a lot better data. And I think that would be incredibly useful for patients as well as clinicians, but particularly patients as they're making decisions about which device they want to use.

DR. BREMER: Thank you. Dr. Gregg.

DR. GREGG: So I agree with these previous comments that it would be really nice to be able to get from this registry better information about how care has changed, how actually patients react and what they do differently, is this actually used as adjunctive or

does it actually end up being their primary -- you know, all those sorts of things. And the proposal that's in the background materials suggests that it would be very detailed and it would give you a lot of that information as well as details about the insertions and removals and all of that. It does seem, though, that the number that's proposed, which I think is 175, is by definition not enough, though, to get, first of all, much diversity, I think. Do you really want to look at, you know, a diverse range of people that are -- that might be using this, that's not going to be enough.

And, secondly, by definition, it's only going to capture fairly common adverse events. If there are more rare ones out there that we haven't thought of and fortunately we haven't seen them, but more rare, severe things, then that number is just not going to give you -- and so I guess what I would propose is that it's nice to have detailed information on a small number, but maybe what could be considered is a focused, detailed set on, for example, a small number like that, but a broader set in a registry for collection for that, for the aspects of diversity and more rare adverse events.

DR. BREMER: Ms. Petersen and then Dr. Wyne.

MS. PETERSEN: Instead of organizing that registry based on a specific number of patients, you could set it up to require a registry of all over a particular period of time, for example, every patient who's implanted over, say, 5 years or 7 years. That would give you significant longitudinal data for longer use periods that might inform people who are really looking at 20, 30, 40 years. It would also help to achieve a diversity goal without trying to cherry-pick certain patients where you might wind up with other forms of bias getting into it, either advertent or inadvertent.

DR. BREMER: Dr. Wyne.

DR. WYNE: You know, your point about the study being too small is a very good point because what's proposed here is 175 patients over 20 sites, so each site is only being

asked to enroll less than 10 patients, so you're not developing expertise at any one site. If each site was doing 20 or 50 patients, then they would truly have expertise and have expertise in dealing with all these things. So that's a concern to me, about the volume of the study, the proposed study.

The idea of doing every patient for the first 5 years, if the usage is the way we think, that would be an unmanageable volume of data. So I don't think we could systematically track every single patient who gets implanted, removed, implanted for a full 5 years, even though I would love to, and when we talk about big data, that would certainly be big data and would be nice, but it still would be nice to have a large cohort who was followed for 5 years, 10 years, etc.

Back to this study proposed, what I like is the inclusion criteria is very -- you know, diabetes adults, period. Obviously, pediatric is a different study. Exclusion is much smaller than it was on the previous ones, so specifically people with known complications are no longer being excluded. But, again, you get back to 175 patients. Well, how many will have retinopathy, how many will have nephropathy? It's not a big enough study to pick up all the complications.

So as you start to think about skin and circulation issues, there are certain groups who really truly do need to be studied, including some excluded here. So just starting with the exclusions, we need a pregnancy study; this would be so valuable in pregnant patients. We need a critical -- hospital study. As Dr. Burr has mentioned many times, we need people who are chronically treated with steroids, which includes our pulmonary patients, our rheumatologic disorder patients; there's a huge body of those patients. And also our transplant patients are often on steroids; that's another group that this would be very valuable to them because doing finger sticks in addition to a dozen meds is challenging.

So transplant, pregnancy, hemodialysis as a separate group from peritoneal dialysis;

again, these are issues with respect to volume. And hydration and microvascular disease. I would also envision that our patients with significant retinopathy, this could improve their quality of life, because if you can't see to poke your finger or get the drop, it's pretty hard to do a finger stick, and so now you're talking about someone just doing a calibration for you; at least you've got information to work from. So I think there's a lot of subgroups that we need to think about, and as Anna mentioned, the hypertensive patient on three to five medications where their volume status changes, and so there's specific subgroups that do need to be assessed over time and couldn't be done in only 175 patients.

DR. BREMER: Dr. Tung.

DR. TUNG: To Dr. Wyne's list I'll add behavior during perioperative care and care in the hospital. There's a lot of potential there. Insulin is a very dangerous drug in the hospital. You could use it better.

DR. BREMER: Yes.

DR. KRAFT: It's Walter Kraft.

So, you know, I've not heard around the table a consensus of, you know, that this would be a vehicle for filling in knowledge gaps, right? And so I've not heard yet a consensus on what specifically knowledge gaps are because we can either do a big study that lightly gathers data to look for specific items, you know, automated -- and efficacy, looking at the data, or you could look at a smaller number much more richly. The question that gets answered in a clinical trial or a registry is the question that's asked. So I guess, for us, maybe much more helpful for the FDA is what is -- if we would prioritize what the gaps are.

DR. BREMER: Thank you. Dr. Wyne.

DR. WYNE: I would say that this proposed study addresses the major pieces of knowledge that need to be known about the device and the use of the device and the

physical use of the device, and I think, for that purpose, the proposed study really does do what we want it to do and probably can be done with that volume. We have lots of other ideas of things we want to see done, but that doesn't have to be done with this study. And I think a registry collects a lot of information that you want, as they showed us from the European registry, which is real-life experience, which has a benefit that you don't get from clinical trials. So I don't think this study should be overloaded with lots of small details, because as I said, it is directing -- addressing the physical issues that we do need more knowledge on.

DR. BREMER: Dr. Lias.

DR. LIAS: This is all helpful information to have. Earlier I heard some mention of discussion when we were talking about the modifications to the blunt dissector, some comments, but I haven't heard comments here about that. It would be helpful to hear, one way or the other, whether -- and what type of information on insertion and removal would be helpful to collect, if any.

DR. BREMER: Dr. Burr.

DR. BURR: Yeah, this is probably on me. I think it would be very helpful to know, in a reliable, sequential way over a substantial number of uses of the device, what the complication rate was, and those complications either occur immediately at the time of the use of the device where an unexpected injury to the skin or subcutaneous tissue takes place or it's an insertion failure for some reason, or an infection. So those are things that are all within several days to a week of the use of the device.

There is a second time downstream, whenever the device is removed, that it would also be good to know if there are issues associated with that, even though they'd be less probable: difficulty within removal, a post-removal infection perhaps, an incomplete removal, fracture of the device. Those are all useful things to know and may lead either to

engineering changes or technique changes or device changes that would improve the record. I think the record is liable to be pretty good out the gate, but we really don't know over a large and diverse group of people, which will be exposed when this device becomes available, the collection of people on which it will be used will be much more substantial, much more diverse than the group studied in the studies. So I think that, simply from the mechanics of starting and stopping a device is important.

There are other -- you know, another aspect of the device that's important is if it doesn't last 90 days, why doesn't it last 90 days? And there you've got questions about average glucose levels during the time of the duration of the sensor; if they're higher, it quits quicker, and that has effects on what the real cycle of the sensor are. Is it truly 90 days, or for the entire patient population, should it be 80 days or 70 days, something like that?

DR. BREMER: Dr. Wyne.

DR. WYNE: Thanks. So, with respect to removal, I was actually reassured when they mentioned that they discovered some of the problems in the fracture was because people were picking their own forceps, whatever device they wanted to try to pull it out. And so now they're supplying a recommended device so that you're exerting an appropriate amount of pressure and maybe not something that's not too pointed on the tips, and that reassured me that possibly part of any removal issues had already been addressed.

(Off microphone comment.)

DR. WYNE: Well, I don't know. How many people have done it with your specifically provided device?

DR. GOODNOW: Yeah, we started that in December, so I don't have a number for you yet.

DR. WYNE: So we don't have data yet.

DR. GOODNOW: Five hundred, a thousand, something --

DR. KELLEY: Five hundred, a thousand --

DR. GOODNOW: Something like that.

(Off microphone comment.)

DR. WYNE: Yeah.

DR. BURR: This is going to be -- you know, you've had a very constrained, carefully supervised and watched group of people who know that they're being watched, so at the very least, there's a Hawthorne effect going on here. But when you throw it out into the general population, not only is the patient base going to be substantially more diverse, your user base, regardless of training, is going to be substantially more diverse and vary a lot in their qualifications and capabilities. And reliance on tools for what is essentially a dexterity-related technique -- helpful, but it doesn't guarantee that there won't be issues downstream. So looking and knowing, I think, would be helpful.

DR. BREMER: Other comments or questions?

(No response.)

DR. BREMER: A very robust discussion, and I very much appreciate it. I'll try to summarize, and again, please, if I omit any key points, please, please clarify with me.

My feeling from the discussion amongst the panelists is that the proposed post-approval study is a great way to begin to elucidate some of the core questions regarding the long-term device, the long-term data regarding usage of the device; however, the Sponsor and the Agency may consider being more cognizant of the acute -- and when I say acute, maybe perioperative -- and maybe longer-term complication or event rates that occur both after sensor insertion and removal, particularly with new devices that will be employed if this moves forward.

And other considerations for the Agency and Sponsor, in any type of post-approval

study, would be the creation or tracking of patients in a certain type of registry, and although the numbers proposed right now may be sufficient to ascertain certain questions, certainly broadening the scope of the patient population, the *n*, if you will, of how many are followed and including different subcategories could be very useful to the clinicians who will be utilizing the device with their patients.

Also, in such registry as far as kind of getting more granular things, the recommendation as far as long-term assessment of plasma dexamethasone, it may not be necessary in a most useful use of resources, however, in at least the short-term, the ascertainment of how much dexamethasone acetate remains on the sensors when they are returned or taken out, to provide more confidence and safety data that there is limited exposure to long-term dexamethasone systemically.

Also, in such a registry, moving forward, in addition to traditional glycemic endpoints, if you will, HbA1c or time in range is certainly -- including patient-reported outcomes and possibly expanding beyond the traditional validated metrics to potentially more app-based methods as seen fit and as seemed would be useful.

And another way to move forward, like my preface at the beginning, as far as other patient populations, as the device is utilized more systemically, to make a concerted effort to capture information long term in those with microvascular complications, hypertension, dialysis, hemodialysis, peritoneal dialysis, and pregnancy as kind of subcategories.

I think the overall discussion was that a lot could be done. What the Sponsor and Agency have seen so far is a great place to start, but how that can be morphed or changed to be practical and useful to the practitioner would be helpful. That was not a very short summary. Did I miss anything?

(Off microphone comment.)

DR. BREMER: Yes, sir?

DR. GRUNBERGER: No, it was superb, but I'm glad you're the Chair. One of the things, going back to Dr. Lias's question, is that since there have been quite a few investigators have used the old tools, then once the new tool gets introduced, it would be nice to be able to go back to these investigators and ask them directly, just to basically see what happened as far as both adverse events but also what their input is back into it because then they can serve as their own control.

DR. BREMER: Thank you, Dr. Grunberger. And I did omit one thing is I'd like to turn to the interventional endocrinologists. I think assessing the clinical satisfaction scale would be very, very useful not just with this system but with other systems that might be coming. So that was very apropos, Dr. Lias, but is that sufficient for you?

DR. LIAS: Yes, thank you.

DR. BREMER: Thank you. Okay, I believe this -- we are now potentially going to get a break, I think. Actually not. We're on a roll here. As a Panel, I want to thank you for the robust discussion. We will now transition to the FDA to ensure that we've done our job for their questions and to give the FDA time to pose any further clarifications to us.

Dr. Lias.

DR. LIAS: I don't have any clarifications on the discussion questions. I appreciate the feedback, and I think we have a lot of food for thought as we work with the Sponsor on discussing the issues that have come up today, so thank you very much.

DR. BREMER: Thank you, Dr. Lias, and thank you to everyone in the FDA for all your work.

I now want to transition to the Sponsor. Thank you for staying and hearing the discussion and being available to clarify questions that came up during the discussion. Are there any points, anything that you feel would be helpful in our deliberations as we move forward to the voting questions that you would like to present to the Panel?

DR. GOODNOW: No. I'd like to first thank the Panel for their time today and the opportunity to take a look at our product. We're obviously very proud of it, and we appreciate your focus and attention to it. We certainly would like to thank the Agency for the support over the last review time period. We recognize that they put a lot of effort and time into helping us bring a new product to market, hopefully to bring it to market. But I also do want to point out a lot of folks that we wouldn't be here without, the folks that are in the clinical trials. They put up a lot of personal time for essentially no compensation to be a part of these studies, and they are very, very rigorous; 16, 18 hours in a clinic, sometimes a couple of times a week, is a very material amount of time, and we very much appreciate them helping us get here as well, so thank you.

DR. BREMER: Thank you. And as Chair I'll reiterate that all of us, I think, really appreciate everything that our participants and our patients do to advance the field. With that, thank you to the FDA, and thank you to the Sponsor.

Before we do proceed to the Panel vote, I would like to ask our nonvoting members if -- and, again, to reiterate for the record, Ms. Carolyn Petersen, our Consumer Representative; Dr. Gabriella Lakos, our Industry Representative; and Ms. Anna McCollister-Slipp, our Patient Representative, not just a sincere thank you for being here and providing your input and your insights, but if there are any further questions or any further comments you would like to present, now would be a good time to. Dr. McCollister-Slipp?

MS. McCOLLISTER-SLIPP: Nothing further for me.

DR. BREMER: Ms. Petersen?

MS. PETERSEN: I'd just like to thank the patients who came today to share their experiences and their stories. As patients, you live with the reality every day, and it becomes very tiresome at times to have to constantly explain things to people. It's very helpful for panels of this nature to hear from users what their experience has been, and I'd

like to thank you.

DR. BREMER: And Dr. Lakos.

DR. LAKOS: I don't have questions. Thank you for the opportunity.

DR. BREMER: Wonderful. I will reiterate again, every patient who participates in these trials, a huge, sincere, and heartfelt thank you.

With that, I will now provide a 10-minute break for everyone. Thank you again for your participation. iPhone says it's 4:02; we're doing well on time. So as far as the panelists, if we could reconvene -- do you people want -- 10 minutes?

CDR GARCIA: 4:15.

DR. BREMER: Fifteen. I'll be generous, 4:15. Fifteen-minute break. If we could reconvene here at 4:15, we will proceed with the voting questions. Thank you all.

(Off the record at 4:02 p.m.)

(On the record at 4:16 p.m.)

DR. BREMER: Thank you, everyone, for coming back. Okay. And since I have you here again, thank you all for being here. This is extraordinarily helpful. All of the discussion all day has been very informative and very useful.

Now we are ready to vote on the Panel's recommendation to the FDA for the Senseonics Eversense Continuous Glucose Monitoring System device. The Panel, our Panel, is expected to respond to three questions relating to safety, effectiveness, and risk versus benefit. Commander Garcia will now read two definitions to assist in the voting process. Commander Garcia will also read the proposed indication for use statement for the device.

Commander Garcia.

CDR GARCIA: Thank you, Chair.

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 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. Subparagraph 860 - 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. Subparagraph 860 - 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.

The Sponsor has proposed the following indications for use: The Eversense Continuous Glucose Monitoring System is indicated for continually measuring glucose levels in adults (age 18 and older) with diabetes for the operating life of the sensor. The system is intended to:

- Aid in the management of diabetes.
- Provide real-time glucose readings.
- Provide glucose trend information.
- Provide alerts for the detection and prediction of episodes of low blood glucose (hypoglycemia) and high blood glucose (hyperglycemia).

The system is a prescribed device. Historical data from the system can be

interpreted to aid in providing therapy adjustments. These adjustments should be based on patterns seen over time.

The system is indicated for use as an adjunctive device to complement, not replace, information obtained from standard home blood glucose monitoring devices.

Panel members, please use the buttons on your microphone to place your vote of yes, no, or abstain in the following three questions.

Voting Question Number 1: Is there reasonable assurance that the Senseonics Eversense Continuous Glucose Monitoring device is safe for patients who meet the criteria specified in the proposed indication?

Please submit your vote: yes, abstain, or no.

(Panel vote.)

CDR GARCIA: Voting Question Number 2: Is there reasonable assurance that the Senseonics Eversense Continuous Glucose Monitoring System is effective for use in patients who meet the criteria specified in the proposed indication?

Please vote now: yes, abstain, or no.

(Panel vote.)

CDR GARCIA: Voting Question Number 3: Do the benefits of the Senseonics Eversense Continuous Glucose Monitoring System outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

Please vote now: yes, abstain, or no.

(Panel vote.)

CDR GARCIA: The votes have been captured, and I will now read the votes into the record.

On Question Number 1, the Panel voted eight yeses, no abstentions, and no noes that the data shows reasonable assurance that the Senseonics Eversense Continuous

Glucose Monitoring System device is safe for determining insulin dose use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted eight yes, no abstentions, and no noes that there is reasonable assurance that the Senseonics Eversense Continuous Glucose Monitoring System is effective for determining insulin dose in patients who meet the criteria specified in the proposed indication.

On Question Number 3, the Panel voted eight yes, zero abstentions, and no noes that the benefits of the Senseonics Eversense Continuous Glucose Monitoring System device to determine insulin dose outweigh the risks for use in patients who meet the criteria specified in the proposed indications.

The three voting questions are now complete. Chair.

DR. BREMER: Thank you to all. I want to thank everyone present at the table, present in the room, all the voting members, nonvoting members. The discussions we had today, I think, were very robust, very informative, and I think will promote a safe and effective use of devices. I appreciate the input of the patients and the participants and everyone, and the Sponsor and the Agency. Everyone gave a lot of time and thoughtful input, and all that will be taken back, and we are very appreciative. It is with that that I have the pleasure of giving you some time back in your day. I'd like to thank the Panel.

(Off microphone comment.)

DR. BREMER: Maybe not, but -- no. Now I can give you time back in your day. Again, I want to thank everyone here, the Sponsor, the Agency, panelists, voting members, nonvoting members, patients, participants, those who had to leave early for various travel accommodations, for all the efforts and everything you do to improve the lives of patients with diabetes and their families; we are extremely appreciative. Thank you.

And, with that, I have also the pleasure of saying, on script, I now pronounce the

Clinical Chemistry and Clinical Toxicology Devices Panel adjourned.

Safe travels, everyone.

(Whereupon, at 4:26 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES PANEL

March 29, 2018

Gaithersburg, Maryland

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.

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SHAYLAH LYNN BURRILL

Official Reporter