FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC) MEETING

Virtual Meeting

Thursday, September 21, 2023

9:00 a.m. to 5:32 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. LOW WANG: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her e-mail is currently displayed.

Thank you for joining the meeting this morning. My name is Dr. Cecilia Low Wang, and I will be chairing this meeting. I will now call the September 21, 2023 Endocrinologic and Metabolic Drugs Advisory Committee meeting to order. Commander Latoya Bonner is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

CDR BONNER: Good morning. I am LaToya Bonner, the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We

will start with our chair, Dr. Low Wang.

DR. LOW WANG: Thank you. My name is Cecilia Low Wong. I'm a professor of medicine and endocrinologist at the University of Colorado School of Medicine.

CDR BONNER: Next, we will have Dr. Greevy.

DR. GREEVY: Good morning. This is Robert Greevy. I'm a professor of biostatistics at Vanderbilt University.

CDR BONNER: Dr. Kalyani?

DR. KALYANI: Good morning. Rita Kalyani. I'm associate professor of endocrinology at Johns Hopkins University.

CDR BONNER: Thank you.

Next is Dr. Wang -- Thomas Wang. Sorry. Dr. Thomas Wang?

DR. WANG: Thank you. Thomas Wang, professor of medicine and a cardiologist at UT Southwestern Medical Center.

CDR BONNER: Thank you, sir.

Next is our industry representative, Dr. Meininger.

DR. MEININGER: Hi. Gary Meininger, FDA industry representative, endocrinologist, and chief medical officer of Sana Biotechnology.

CDR BONNER: Thank you.

Next is our patient representative, Ms. Barbara Berney.

MS. BERNEY: Good morning. I am just a patient representative. This is Barbara Berney.

CDR BONNER: Thank you, ma'am.

Next we have Dr. Erica Brittain.

DR. BRITTAIN: Hi. I'm Erica Brittain. I'm a statistician at the National Institute of Allergy and Infectious Diseases at NIH.

CDR BONNER: Thank you.

Next is Dr. Burman.

DR. BURMAN: Good morning. Ken Burman. I'm on the staff at Medstar Washington Hospital Center and a professor at Georgetown University.

CDR BONNER: Thank you.

Dr. Cooke?

DR. COOKE: Good morning. I'm David Cooke. I'm an associate professor of pediatrics in the

Division of Pediatric Endocrinology at Johns Hopkins.

CDR BONNER: Thank you.

Dr. Crandall?

DR. CRANDALL: Hi. I'm Jill Crandall. I'm a professor of medicine and chief of endocrinology at Albert Einstein College of Medicine.

CDR BONNER: Thank you.

Next is Dr. David?

DR. DAVID: Good morning. I'm a biomedical engineer and principal at Biomedical Engineering Consultants in Houston, Texas.

CDR BONNER: Thank you.

Dr. Everett?

DR. EVERETT: Good morning. My name is Brendan Everett. I'm associate professor of medicine at Harvard Medical School and a cardiologist at the Brigham and Women's Hospital in Boston, Massachusetts.

CDR BONNER: Thank you.

Next is Dr. Kagan.

DR. KAGAN: Good morning. I'm Leonid Kagan,

associate professor in pharmaceutics, Rutgers University in New Jersey.

CDR BONNER: Thank you, sir.

Next is Dr. Konstam.

DR. KONSTAM: Hi. Mark Konstam. I'm a cardiologist, and I direct the CardioVascular Center at Tufts Medical Center in Boston.

CDR BONNER: Thank you.

Next is Dr. Munir.

DR. MUNIR: Good morning. Kashif Munir. I'm an adult endocrinologist at University of Maryland.

CDR BONNER: Thank you.

Dr. Nachman?

DR. NACHMAN: Yes. Good morning. Patrick Nachman. I'm a nephrologist. I'm a professor of medicine and director of the Division of Nephrology and Hypertension at the University of Minnesota.

CDR BONNER: Thank you, sir.

Next we have Dr. Nason.

DR. NASON: Good morning. Martha Nason. I'm a mathematical statistician at the National

Institute of Allergy and Infectious Diseases, NIH.

CDR BONNER: Thank you.

Next is Dr. Newman.

DR. NEWMAN: Good morning. I'm Dr. Connie Newman. I'm an endocrinologist and adjunct professor of medicine in the Division of Endocrinology, Diabetes and Metabolism at the New York University School of Medicine.

CDR BONNER: Thank you, ma'am.

Next is Dr. Weber.

DR. WEBER: Hi. This is Tom Weber. I'm a professor of medicine in the Division of Endocrinology, Metabolism and Nutrition at Duke University Medical Center in Durham, North Carolina.

CDR BONNER: And next, we will have Dr. Wilson.

DR. WILSON: Good morning. Peter Wilson, a professor of medicine and public health, endocrinology and cardiology research at Emory University.

CDR BONNER: Thank you, sir.

We will now move to our FDA participants. When I call your name, please go to the podium and introduce yourself to the audience, for the record. We will start with Dr. Peter Stein.

DR. STEIN: Good morning. Peter Stein, director of the Office of New Drugs, CDER, FDA.

CDR BONNER: Thank you.

Next is Dr. Joffe.

DR. JOFFE: Good morning. I'm Hylton Joffe. I'm the director of the Office of Cardiology, Hematology, Endocrinology, and Nephrology in the Office of New Drugs, CDER, FDA.

CDR BONNER: Thank you.

Next is Dr. Yanoff.

DR. YANOFF: Good morning. I'm Lisa Yanoff. I'm deputy director in the Office of Cardiology, Hematology, Endocrinology, and Nephrology, Dr. Joffe's office, in CDER, FDA.

CDR BONNER: Thank you.

Next is Dr. Sharretts.

DR. SHARRETTS: Good morning. I'm John Sharretts. I'm the director of the Division of

Diabetes, Lipid Disorders, and Obesity.

CDR BONNER: Next is Dr. Archdeacon.

DR. ARCHDEACON: Good morning. I'm Patrick Archdeacon, deputy director in the Division of Diabetes, Lipid Disorders, and Obesity.

CDR BONNER: Next we have Dr. Carey.

DR. CAREY: Good morning. I'm Michelle Carey, associate director for Therapeutic Review in DDLO, OCHEN, and CDER, FDA.

CDR BONNER: Next we have Dr. Penzenstadler.

DR. PENZENSTADLER: Hi. Good morning. My name is Justin Penzenstadler. I'm a clinical team leader in the Division of Diabetes, Lipid Disorders, and Obesity, CDER, FDA. Thank you.

CDR BONNER: Thank you.

Next is Dr. Wolloscheck.

DR. WOLLOSCHECK: Good morning, everyone. My name is David Wolloscheck. I am the assistant director in the General Hospital Devices Team in CDRH.

CDR BONNER: Thank you.

Next we have Dr. Chow.

DR. CHOW: My name is Dr. Edwin Chow. I'm a clinical pharmacology team leader at Office of Clinical Pharmacology.

CDR BONNER: Thank you, sir.

Next is Dr. Tu.

DR. TU: Hi. My name is Wenda Tu. I'm the statistical reviewer from Division of Biometrics II, Office of Biostatistics.

CDR BONNER: We have now concluded the meeting roster. I will go ahead and turn the floor back over to our chair, Dr. Low Wang.

DR. LOW WANG: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

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

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

Commander Bonner will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you. LaToya Bonner.

The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry

representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that that agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is

not so substantial as to be deemed likely to affect the integrity of the service which the government may expect from the employee.

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

Today's agenda involves discussion of the safety and efficacy of ITCA 650, exenatide in DUROS device, a drug-device combination product that is the subject of new drug application submitted by Intarcia Therapeutics, for the proposed indication, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CDER is holding this meeting pursuant to a March 24, 2023 letter from the chief scientist of FDA, Dr. Namandjé N. Bumpus, wherein she granted Intarcia's request under 21 CFR 12.32(b)(3)(ii) for a public hearing before an advisory committee in lieu of a formal evidentiary hearing. Intarcia requested a public hearing before an advisory committee on CDER's proposal to refuse approval of Intarcia's NDA for ITCA 650. This is a particular matters meeting during which specific matters related to Intarcia's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that

Dr. Gary Meininger is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Meininger's role at this meeting is to represent industry in general and not any particular company. Dr. Meininger is employed by Sana Biotechnology.

We would like to remind members and temporary voting members 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 committee of any financial relationships that they may have with the firm at issue.

Thank you. I will now turn the meeting back over to our chair.

Dr. Low Wang?

DR. LOW WANG: Thank you, Commander Bonner.

We will now proceed with FDA introductory

remarks from Dr. Patrick Archdeacon.

FDA Introductory Remarks - Patrick Archdeacon

DR. ARCHDEACON: Good morning. I'm Dr. Patrick Archdeacon, deputy director of the Division of Diabetes, Lipid Disorders, and Obesity. I'd like to thank the members of the advisory committee, my FDA colleagues, the applicant, and patients with type 2 diabetes for attending and participating in today's meeting.

CDER has convened this meeting to discuss the safety and efficacy of ITCA 650, also known as exenatide in DUROS device, a drug-device combination product submitted for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. CDER assesses the new drug application for ITCA 650 is not approvable in its current form because the benefit-risk assessment for the product is unfavorable, based on the available data.

The applicant requested a public hearing before an advisory committee on CDER's proposal to

deny approval of the application. CDER is holding this AC meeting pursuant to a letter from the FDA chief scientist, wherein she granted the applicant's request for a hearing before an AC.

Type 2 diabetes affects around 37 million Americans. Patients with type 2 diabetes are at an increased risk for debilitating microvascular and macrovascular complications. Intensive glycemic control measured by A1C reduces the incidence of microvascular complications. Treatment guidelines also recognize the crucial role of patient behaviors and preferences, including adherence to medications, in the management of type 2 diabetes.

Despite a substantial therapeutic armamentarium, up to half of patients with type 2 diabetes do not achieve glycemic targets, illustrating the need for additional treatment options that are safe, effective, and improve adherence.

In recent years, novel therapeutic drug classes that improve glycemic control have been added to the diabetes armamentarium and have

supplanted older therapies and professional society clinical guidelines and recommendations. These recommendations are informed by data from large cardiovascular outcome trials, or CVOTs, and renal outcome trials. Those trials also resulted in additional indication for the reduction of major adverse cardiovascular events, or MACE, hospitalization for heart failure, and renal events in adults with type 2 diabetes for certain SGLT2 inhibitors and GLP-1 receptor agonists that have established benefits beyond glycemic control.

GLP-1 receptor agonist products are generally characterized by robust efficacy, as measured by improvement in glycemic control, and most GLP-1 receptor agonist products are also associated with body weight loss. Several GLP-1 receptor agonist products have demonstrated statistically significant benefits in reducing MACE. The cardiovascular trials of several other GLP-1 receptor agonists yielded hazard ratios for MACE below 1 but not reaching a statistical significance. Although the blood glucose lowering

and weight loss are better understood, the mechanism responsible for the observed cardiovascular benefit has not yet been fully elucidated.

Byetta, an immediate-release formulation of exenatide, was the first approved GLP-1 receptor agonist product. It was approved in 2005 as a twice-daily injection to improve glycemic control in adults with type 2 diabetes. In the following years, seven more GLP-1 receptor agonist products have been approved. Bydureon, an extended release formulation of exenatide, was approved in 2012 as the first once-weekly injection. Rybelsus was approved in 2019 as the first orally administered GLP-1 receptor agonist product. After full review of the respective completed cardiovascular outcome trials, Victoza, Ozempic, and Trulicity received an indication to reduce the risk of MACE.

ITCA 650 is a drug-device combination product. It contains a different exenatide formulation from the formulations approved as Byetta and Bydureon. Although exenatide is not a

new molecular entity, ITCA 650 is a new drug product. The proposed dosing regimen is a device that is stated to deliver 20 micrograms per day of exenatide for 3 months, followed by titration to a device stated to deliver 60 micrograms per day of exenatide for 6 months. The 60-microgram per day device is intended to be removed and replaced every 6 months thereafter.

Based on review of the data submitted to the NDA, CDER concluded that the in vitro studies showed that release of exenatide was inconsistent, fluctuating between periods of under-delivery and over-delivery. The PK data was consistent with the in vitro studies. Observed exposures were variable and featured occasional sudden large increases.

Estimating the treatment effect of ITCA 650 was challenging because of an unusually large amount of missing endpoint data in the glycemic control trials; however, the FDA statistical reviewers arrived at an estimated treatment effect of 0.7 percent reduction in A1C compared to placebo, which FDA recognizes as clinically

meaningful. Review of the clinical safety data showed unfavorable imbalances in acute kidney injuries, AKI, MACE events, overall serious adverse events, and all-cause mortality. Most of the serious AKI events were preceded by gastrointestinal events, and meta-analysis indicates that the ITCA 650 CVOT is an outlier among the GLP-1 receptor agonist CVOTs.

The device issue, along with the finding of variable PK with rapid fluctuations and the available clinical safety data, raise uncertainty about the safety profile of ITCA 650. The safety signals associated with ITCA 650 should be addressed with submission of additional premarket data.

Patient adherence is a critical clinical issue; however, the potential for improved adherence among individuals who might prefer biannual medical procedures versus a once-weekly self-administered injection or a daily oral medication needs to be balanced against any additional risks associated with the drug,

especially because evidence that this implantable device for the treatment of type 2 diabetes will translate into improved long-term outcomes is lacking.

Overall, CDER concluded that the benefit-risk assessment for this product is unfavorable based on the available data. CDER again thanks the advisory committee for their attendance and participation. We will have the following charge to the committee.

Discuss your assessment of the safety profile of ITCA 650 and whether the safety profile of the ITCA 650 drug-device combination product has been adequately characterized based on available data, with respect to acute kidney injury, with respect to cardiovascular safety, and with respect to overall safety.

Discussion question 2, discuss your assessment of the benefit-risk balance of ITCA 650 for the indication to improve glycemic control in patients with type 2 diabetes. And finally, at the end of the day, we'll ask a voting question. The

committee will be asked to vote on the following question.

Based on the available data, has the applicant demonstrated that the benefits of the ITCA 650 drug-device combination product outweigh its risks for the treatment of type 2 diabetes? Committee members will also be asked to provide a rationale for their vote. Should a member vote no, CDER asks that the member also comment on additional data that could be provided to demonstrate that the benefits outweigh the risks.

That concludes my introductory statement. Thank you.

DR. LOW WANG: Thank you, Dr. Archdeacon, for that introduction and overview.

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

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

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

We will now proceed with the presentation by Intarcia Therapeutics.

Applicant Presentation - Kurt Graves

MR. GRAVES: Good morning, Madam Chair, members of the advisory committee, and members of the FDA. I'm Kurt Graves, former chairman and CEO of Intarcia Therapeutics, and now chairman,

president, and CEO of i2o Therapeutics, where Intarcia is an acquired business unit. We appreciate the opportunity for this meeting and for the independent review of the data by the committee to resolve the disputed issues and gain your perspective on patient needs and the benefit-risk profile of ICA 650.

When our original EMDAC request in 2020 was denied by CDER, the company and our external scientific advisory board jointly filed the factual inaccuracies in a public and transparent forum, along with a formal request for a public hearing with the commissioner in March of 2021.

Importantly, the disputed issues and facts that will be presented today are the same facts that compelled the Commissioner's Office and FDA's chief scientist, Dr. Bumpus, to grant today's hearing before the EMDAC after they had completed a detailed side-by-side review of disputed issues and facts submitted by Intarcia versus CDER's asserted six denial issues. We sincerely thank them for their objective review of the facts and seeing the

need and benefit of holding this unique hearing. There are very few such hearings granted by the highest offices of the FDA.

On February 8th this year, the Commissioner's Office and Chief Scientist Bumpus concluded their review of the disputed facts and granted this hearing with a letter stating, and I quote, "I have identified numerous disputes in the materials submitted between the parties, and I believe that a public hearing before an advisory committee could aid in the resolution of the parties' disputes and enable the commissioner to render a final decision for the agency on this matter."

Unlike a normal EMDAC designed to give your advice to CDER, here your independent review of the facts and advice will go to the Commissioner's Office and Dr. Bumpus, who will treat your input as an initial decision. Dr. Bumpus and the Commissioner's Office will be making the final benefit-risk decision for ICA 650, so within this framework, let me start by describing ICA 650.

ICA 650 delivers exenatide, an already approved GLP-1, which has a well known benefit-risk profile and has been used to treat patients with type 2 diabetes since 2005. The two main exenatide brands on the market right now are Byetta, injected twice daily, and Bydureon, which is injected once weekly.

Note that the two exenatide products and all approved GLP-1 medications each have a labeled warning for serious AKI events associated with GI adverse events and dehydration. The AKI warnings were based on thousands of GLP-1 postmarketing AKI events and represent a class effect that we will show today have been reported in multiple large randomized trials for GLP-1s, not ITCA 650 alone.

ITCA 650 delivers exenatide in a match-stick size osmotic implant with important safety features engineered into it. The ITCA 650 exenatide implants build upon well-understood osmotic delivery principles used in the previously approved DUROS implant systems that were used for Viadur, a prostate cancer medicine which was marketed for

years safely and effectively until the sponsor exited the therapeutic area. That is when Intarcia acquired the DUROS implant technology for use in diabetes and other chronic diseases.

Given CDER's focus on the risk of dose dumping, something that has never occurred, and extensive testing of tens of thousands of our implants, it is important to understand that the implant's inherent safety features prevent risk of bolus drug release. The ITCA 650 implants consist of a cylindrical titanium alloy reservoir capped on one end by a rate-controlling, semi-permeable membrane, and on the other end by a diffusion moderator assembly with an outlet channel through which drug is released.

On the left side of the implant, the semi-permeable membrane is rated to withstand 710 pounds per square inch of pressure without backing out of the device, which would make it static. This preventive fail-safe is well beyond the pressures attainable by the body at any temperature or hydration level. On the other end

of the implant is a diffusion moderator, which has a much higher psi fail-safe that prevents dislodgement from the implant's drug reservoir, in gray. The diffusion moderator withstands at least 6400 psi, which is around 10x higher than the intake membrane.

This aspect of the fail-safe means that if pressure ever exceeds 710 psi, it will make the intake membrane back out of the device first and render a static device with no risk of diffusion moderator dislodging or dose dumping. This fail-safe has never happened, but it is there to ensure dose dumping will not occur. Lack of dose dumping is also supported by the consistent and sustained efficacy in trials and by the very low incidence of GI adverse events after dose initiation and dose escalation during maintenance therapy in all of our studies.

Today, we'll provide data to support the committee's determination of a benefit-risk profile for ITCA 650 and show the safety profile has been adequately characterized. For the benefit-risk

assessment, it's important to consider the need for a twice-yearly maintenance option for some patients with significant adherence issues. It is also important to consider the consistent efficacy demonstrated across four successful phase 3 trials.

The overall safety profile is demonstrated by rates of SAEs and deaths that were relatively low and comparable to placebo. Safety was in line with the GLP-1 class with early GI adverse events and a small numeric imbalance in serious AKI in 1 of 4 trials, which is also observed for other GLP-1s in both postmarketing reports and randomized-controlled trials we will show. The risk of MACE is characterized by meeting the FDA's preapproval CVOT requirements and a post-approval of CVOT is warranted, given no CV harm has ever been seen in larger, longer duration, and more definitive trials for exenatide and the entire GLP-1 class.

Here is a brief summary of the six prioritized issues in CDER's proposed order to deny approval of ITCA 650. The hearing process and your

feedback going back to the Commissioner's Office requires us to stick to the disputed facts on each of CDER's six prioritized issues. These issues from CDER boil down to two main focus areas noted on the slide, which are covered in a different sequence in the division's briefing materials and presentation today.

The most important factual issues to resolve today, though, are related to clinical safety; in particular, whether or not infrequent serious AKI events associated with GI side effects and dehydration are a GLP-1 class effect, or somehow, despite the same biological mechanism for the class, solely isolated to an already approved GLP-1 in ITCA 650 exenatide.

The second grouping of issues is around the implant drug delivery and whether or not the clinical trial data in four positive phase 3 trials has provided clinical validation of the implant release specifications as effective and safe for their intended and labeled use in a reliable manner.

Let's start with framing AKI, the number one issue. There are two key AKI assertions that are the crux of CDER's proposed denial of ITCA 650. The first and most important issue for this entire hearing is that the review division contends there are no clinical trial evidence of any small unfavorable numeric imbalances in AKI SAEs versus placebo for the entire GLP-1 class. The second point from the review division is a related contention that a small numeric AKI imbalance in a randomized trial setting is isolated to ITCA 650 alone in the GLP-1 class.

Both of these contentions are under dispute and need to be factually resolved today because they are tightly connected, and because both are used as the primary justification to reject ITCA 650 and not grant a class-labeled AKI warning, as has been done for all other approved GLP-1s

The evolving AKI evidence for the class shows serious AKI events are associated with GI side effects and dehydration, a class effect and a shared biological mechanism across the class that

is not isolated to only one product, as CDER contends. In fact, over the past six years, the understanding of AKI has evolved with numerous publications, FDA documents, and sponsor AKI documents showing GI AES are linked to AKI events from clinical trials and postmarketing events.

This evolution of evidence has even caused a new FDA review team to update the most recent GLP-1 AKI warnings granted to include two new facts that are important today. The new warning for AKI granted to Wegovy states that AKI imbalances have occurred in their clinical trials in the NDA, and two, that AKI imbalances were associated with GI side effects and dehydration right in the Wegovy AKI warning language.

Let's look at the evolution of this serious AKI evidence and labeling evidence I just talked about. In 2009, serious AKI events were first identified and labeled as a serious potential risk for the class due to postmarketing serious AKI reports. In these five, high-profile GLP-1 trials, there is now mounting, on-treatment, serious AKI

numeric imbalances noted in the public domain. The left side of the slide shows the first three GLP-1 cardiovascular outcome studies with serious AKI imbalances that occurred in 2017. Two of those NDA applications for liraglutide and semaglutide were approved that year with AKI warnings, while ITCA 650 was rejected without an AKI labeled warning.

Since additional serious AKI numeric imbalances in clinical trials have been reported -- for example, in the semaglutide 2.4-milligram NDA with the STEP-2 trial in obesity and type 2 diabetes, and just recently in the last few weeks in the STEP-2 heart failure trial in obesity -- as noted, serious AKI imbalances in multiple semaglutide trials led to a new AKI warning in 2021, which for the first time stated, and I quote, "AKI has occurred in clinical trials" at a higher incidence on drug versus placebo and in association with GI AES and dehydration. That type of label would also be appropriate for ITCA 650.

Taken together the AKI imbalances, a new AKI

warning evidence contradicts each of the two fundamental reasons CDER asserted they were rejecting ITCA 650. It is also noteworthy that a new review team in the division has set a precedent for new AKI warnings, acknowledging that AKI imbalances have occurred in GLP-1 clinical trials. Based on the evolution of AKI evidence and AKI labels, this hearing is a key moment where we can all, and should all, move in a clear direction of acknowledging serious AKI as a class effect that is infrequent but very important risk for the GLP-1 therapy that is associated with GI side effects and dehydration.

Acknowledging this risk as a a class effect, including in clinical trials, allows it to be more clearly communicated as a risk, which needs to be more closely monitored, mitigated, and prevented. This would protect patients and further improve the benefit-risk profile of all GLP-1s, including ITCA 650.

As mentioned, ultimately, the Office of Commissioner and Dr. Bumpus will need to render a

decision based on the six issues identified in CDER's proposed order. We will review the data for each of these three clinical- and device-related issues throughout the remainder of our presentation. Let me briefly address items 4 through 6 here, as we won't return to these items unless they come up in Q&A. These issues involve factual clarifications regarding manufacturing and device items. All have been fully addressed on record with the agency.

First, ITCA 650 implants did perform within their prespecified in vitro release upper and lower limits. Second, for device reliability, we've done the dFMEA work and identified and mitigated device failures to a very low rate of just 0.26 percent, included in our NDA submission. Third, on device quality controls, our manufacturing controls, and the fact we X-ray every single implant in our finished goods, has ensured that we've never had a single empty device in the whole history of the program, which includes many thousands of devices tested in our IVR systems and tens of thousands

more in our four successful phase 3 trials.

Lastly, I must clarify the inaccurate contention CDER raised in their briefing book that sterility deficiencies remain unresolved, that led to a clinical hold in 2017. As you can see in this quote in the middle of this page, the FDA lead manufacturing inspector reported in 2020, when he was doing an inspection, that he reviewed all investigations conducted for the one-time, out-of-spec event that was found to be due to new faulty testing equipment installed at Catalent Labs.

During our last preapproval manufacturing inspection, the FDA's own lead investigator noted in the FDA's official report, and I quote, "I reviewed the sterility failure investigations for the sterility failures that occurred in 2017 and led to the clinical hold being placed on the firm. I reviewed all investigation conducted at Catalent and Intarcia. The investigation appeared to be completed. Raw data were reviewed. CAPAs taken to address the clinical hold were reviewed and found

to be acceptable. No sterility deficiencies were noted."

While the clinical hold remains, it has nothing to do with sterility deficiencies. There are none, per the FDA's own inspector report. The registration studies were completed successfully, and our focus is on resolution of these types of continued factual inaccuracies. CDER is fully aware of these facts in that we've previously communicated we intend to address the hold once this hearing proceeding is finished.

Let's shift from issues now to discuss why we're all here today and why a new extended maintenance dosing option would be a very important opportunity for segments of patients with poorly-controlled glucose.

ITCA 650 would be the first and only maintenance therapy option with a twice yearly dosing interval that is administered and controlled by healthcare providers during routine office visits. ITCA 650 was designed with input from patients and from our scientific advisory board

over the last 15 years to help address the crisis of poor glucose control and adherence challenges that exist in large and growing portions of patients across our nation. The fact is, more than 45 new tablets and injections have been approved in diabetes over the last 15 years, and for some patients, they've brought tremendous benefit. Yet, at least 50 percent of patients in type 2 diabetes remain with uncontrolled glucose that is largely due to nonadherence.

Notably, over 30 percent of patients in the U.S. still have dangerously high glucose with HbA_{1c} levels chronically over 9 percent. Even with the availability of new type 2 diabetes treatment products with oral or injectable administration, adherence, defined as abiding by your prescribed medication schedule at least 80 percent of the time, remains low, by 12 months on therapy as shown here. This was data presented at a prior ADA meeting that underlines adherence is the key issue leading to uncontrolled glucose in millions of patients with type 2 diabetes. At best, within

just 6 to 12 months, one-half to two-thirds of patients are not adherent with their daily or weekly injectable GLP-1s.

Another way of looking at adherence is through persistence gaps on weekly GLP-1 therapies. This slide shows persistence rates in 6-month and 12-month cohorts with two widely used GLP-1s, dulaglutide and semaglutide. For the first 6-month cohort, we see that up to 38 percent of patients have a 40-day gap in persistence in taking their medication. By 12 months, we see upwards of 55 percent of patients having persistency gaps of 60 days.

Just imagine the potential adherence and persistence if a doctor had the option to give ITCA 650 once every 6 months to patients in need during each of these two 6-month time frames? While ITCA 650 is not for every patient, every doctor managing diabetes has patients in their practice where a twice yearly dosing option would be a welcomed and highly relevant solution.

When reviewing the issues and facts today,

we must keep at the forefront of our minds the needs of these patients and the robust efficacy profile of ITCA 650, which is not disputed by the agency and which contribute to the determination of an overall positive benefit-risk profile. There's a serious public health crisis in diabetes related to poor glucose control in at least 20 million Americans. A new and extended dosing option could help address this crisis, and I'm sure we will hear about this today in today's open public forum.

ITCA 650 implants have demonstrated unequivocal and sustained efficacy in all four phase 3 trials in more than 5800 patients, which includes more than 22,000 implants. The extensive clinical data validated the implant release specification limits are indeed effective and safe for their intended use, and they will show an overall PK profile and PK variability that is comparable to exenatide delivered by Bydureon once-weekly injections. And lastly, we'll share the data today supporting the safety profile is fully in line with approved GLP-1s and

class-labeled AKI warnings, and that a post-approval CVOT is warranted, having met FDA's preapproval primary endpoint requirements.

With this information in mind, here is the agenda for the remainder of the presentation. Two external experts in endocrinology, GLP-1 science, and cardiology, Dr. Daniel Drucker and Dr. Philip Sager will join me to review the AKI and MACE issues. We will also have additional subject matter experts with us today to take your questions during Q&A.

Thank you. I'll now turn the presentation to Dr. Drucker, who has been a key leader of the ITCA 650 external scientific advisory board for the last 15 years.

Thank you, Dr. Drucker.

Applicant Presentation - Daniel Drucker

DR. DRUCKER: Good morning, and thank you. I'm Daniel Drucker, professor of medicine at the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital at the University of Toronto. I have no financial interest in today's outcome. I have not

been compensated for my time or expenses and have no interest in the future outcome of this product financially.

I've been studying the actions of GLP-1 since the inception of the field about 35 years ago and have participated in many of the efforts to develop GLP-1-based medicines for people living with type 2 diabetes. I've spent more than three decades elucidating the mechanisms of GLP-1 action and the benefits and risks associated with this class. I do understand the struggle so many people living with type 2 diabetes continue to have controlling their glucose levels simply due to poor treatment adherence. I'll begin this morning with a review of the development program and efficacy outcomes, lending important context to the benefits of ITCA 650.

ITCA 650 has been assessed in more than 5800 patients within a robust clinical development program. Shown here are the five studies supporting this application. For today's presentation, we'll focus on data from randomized

Studies 103, 105, and 107. The randomized studies followed a traditional design for type 2 diabetes trials. Patients were randomized to ITCA 650, started at a dose of 20 micrograms per day or randomized placebo, and then followed for 13 weeks. Individuals were then uptitrated to a once-every-6-month maintenance dose at a nominal dose of 60 micrograms per day.

The endpoints in Studies 103 and 105 were common and well accepted in diabetes studies. The primary endpoint was change from baseline in hemoglobin A1C. The secondary endpoints assessed weight reductions. The CVOT was designed much like other preapproval CVOTs.

As the FDA's briefing book noted, the unequivocal and sustained efficacy with ITCA 650 is not disputed. All randomized control studies met their prespecified efficacy endpoints, demonstrating statistically significant and clinically meaningful reductions in A1C body weight and key A1C treatment targets. The primary safety endpoint for Study 107 was also met. ITCA 650

devices performed exactly as designed, with consistent and highly effective exenatide delivery.

When comparing the placebo in gray and sitagliptin in orange, the HbA_{1C} endpoint was statistically significant across all three randomized studies, showing meaningful and sustained reductions. All three studies also met secondary efficacy endpoints, showing statistically significant change from baseline in body weight. Thousands of ITCA 650 devices used resulted in highly consistent and effective body weight reduction versus comparators.

To contextualize this efficacy, here are the ITCA 650 HbA_{1C} lowering results from baseline levels to end of study, alongside exenatide injections, as shown with Bydureon and other approved GLP-1 receptor agonists. What distinguishes ITCA 650 is its twice yearly dosing option for those people who don't stay on their weekly injections.

I'll now review the safety data. Here's the pooled safety profile across Studies 103, 105, and 107. As expected, more treatment-emergent AEs,

severe AEs, and AEs leading to discontinuation were reported on ITCA 650 compared to pooled placebo. The rates and types of adverse events are in line with the well-established safety profile of exenatide and other GLP-1s. The most common adverse events in more than 5 percent of patients were mostly mild-to-moderate gastrointestinal adverse events. These were transient in nature and generally resolved within a few weeks after initial dosing. The incidence of major hypoglycemia was 0.3 percent in ITCA 650-treated treated patients, only observed when ITCA 650 was used in combination with either sulfonylureas or insulin.

Given the well-known glucose-dependent mechanism of action of all GLP-1s, ITCA 650 and GLP-1s, in general, are not associated with a risk of hypoglycemia when used without concomitant insulin or SUs. Because transient GI AEs represent the predominant side effects seen with all GLP-1 drugs, patients will be informed of the risk of AES at dose initiation and at dose uptitration. Risk factors will also be well outlined in product

labeling.

Clinicians understand that dehydration leading to hypovolemia often results from GI AEs that are severe that can occur with GLP-1 medicines. As a result, all GLP-1 products carry a warning for AKI risks related to transient GLP-induced GI AEs and dehydration, along with other background risk factors. These include pre-existing renal impairment, GI AEs in those already on metformin, and renal risks from diuretics, ARBs, ACE inhibitors, and NSAIDs.

This is precisely why FDA's current AKI warnings for the GLP-1 class state, "Monitor renal function when initiating or escalating doses of GLP-1 in patients reporting severe adverse GI reactions." The overall safety profile remains consistent across the GLP-1 class with all GLP-1 trials reporting adverse events consisting mostly of nausea, vomiting, and diarrhea. These GI AEs also represent the primary cause for product discontinuation.

Importantly, the rate of GI AEs and

discontinuations with ITCA 650 is very similar to that of other available products. AKI warnings were first established based on AKI reports from postmarketing data. In this slide, we show FAERS pharmacovigilance data reporting AKI events for five GLP-1 products since 2005. Notwithstanding the limitations of the FAERS data that we all recognize, there are several thousand GLP-1 AKI reports here. The related complications and outcomes are shown on the right-hand side of the bar graph.

From a recent independent academic publication describing GLP-1-related AKI events within the FAERS database, we also see the consistent temporal relationship occurring early between AKI events and dose initiation and escalation; the times we know precisely when GI AEs typically occur. As stated in the FDA's GLP-1 class warnings, "A majority of the reported AKI events occurred in patients who had experienced nausea, vomiting, or diarrhea, leading to volume depletion."

Here, we show the ITCA 650 GI AE data for nausea, vomiting, and diarrhea over time, relative to reported serious AKIs. The imbalance in serious AKI is observed early on during dose initiation and dose escalation. Indeed, 7 of the 11 serious AKI events on ITCA 650, as shown in purple, occurred at this time compared to only one serious AKI event in people receiving placebo, in yellow. Then when rates of GI AEs decline after dose escalation, the AKI events become dispersed and are not associated with implant changes. Of note, the second-to-last AKI event on the right side of the slide was due to a major GI bleed and not drug related, so the fatality of the event shows that they were balanced with placebo during maintenance therapy.

Transient GLP-1 GI AEs leading to dehydration represent a mitigatable risk for AKI. With label warnings and proactive education, these events can be monitored and mitigated across the class. Clinicians should inform patients with renal impairment about the risk of GI AEs and the subsequent risk of AKI and take proactive action to

avoid dehydration. One can monitor renal function and monitor the extent of transient GI AEs when both initiating and escalating dosing.

Additionally, ITCA 650 will be administered in trained certified offices, where education and risk mitigation measures can be effectively implemented right at the time of dose initiation and dose uptitration. Additional medical staff and online training and video support will also be available to healthcare providers.

With this background on ITCA 650, let's contextualize the risk of AKI in relation to the GLP-1 class. Here's a breakdown of the AKI SAEs. In Study 107, there were 11 treatment-emergent AKI SAEs reported on ITCA 650 compared to four in the placebo group. This is an incidence rate of 0.5 percent versus 0.2 percent, which is not a statistically significant imbalance.

Of the 11 ITCA 650 treatment-emergent AKI events, all patients recovered, with six remaining on therapy and completing the trial. In contrast, and very unfortunately, 2 of the 4 serious AKI

events on placebo resulted in deaths. Two additional serious AKI events were reported that, per protocol, were not treatment emergent since one occurred just prior to the first insertion of ITCA 650 and the other event occurred over 6 weeks after the final removal of ITCA 650. In addition, no GI AEs were involved in these events.

In Study 105, one patient had an AKI SAE that the investigator found was not study drug related. In CDER's briefing document, they note an additional two non-serious AKI events that resulted in death, suggesting that this may drive the imbalance to 60 events for ITCA 650. I'll review these cases in a moment to show that they are consistent with their independent adjudication of not being related to study drug.

In both of the non-serious AKI cases, there were pre-existing risk factors for AKI, and the investigators attributed the causes of death either to multi-organ dysfunction syndrome in the first case, and a major CV event in the second case. The first patient experienced a non-serious AKI due to

viral gastroenteritis, causing dehydration on day 649, which resolved on day 652. No action was taken with regard to study medication, and the investigator confirmed that the viral gastroenteritis and transient associated dehydration was not related to the study drug.

Approximately 100 days later, the same patient was hospitalized for chest pain and admitted with a diagnosis of non-STEMI. After admission, a secondary AKI was diagnosed and the patient received urgent treatment prior to being transferred to another hospital the same day for more evaluation.

Upon admission, the patient had hematemesis, and an endoscopy showed the patient was having AKI caused by a significant ongoing major GI bleed with an associated hemoglobin of 7.2. This ongoing bleed and the associated AKI resulted in the need for dialysis. The case was further complicated by multi-organ dysfunction syndrome that progressively worsened, and, sadly, the patient died on day 755. The case was not drug related, and there were no

proximal GI AEs involved with any of the events on day 747 or thereafter.

The second patient death was from an acute coronary event. This patient had a history of chronic kidney disease and worsening renal function over time. This was a non-serious AKI with no GI AEs reported. The patient was instructed accordingly to stop metformin. On day 119, the family was with the patient in the morning and found him deceased later in the day at their home. The death was due to an acute coronary event, and investigators confirmed that it was not related to study drug.

Contrary to what the review division has asserted in their briefing book for the first time, neither of these cases involved deaths related to the study drug, and both records on file show that there were no proximal GI AEs.

Let's now review the reported 11 different emergent AKI SAEs. Here's the first half of the 11 subjects from Study 107 who experienced the treatment-emergent serious AKI, ordered on this

slide by time to onset. You can see in yellow that 100 percent of patients had both the known underlying AKI risk factors that CDER has used to grant GLP-1 class-labeled AKI warnings. All 11 patients had pre-existing renal impairment at baseline and all were on one or more concomitant medicines that may be associated with increased AKI risk. Again, all of these events resolved.

Here are the remaining 5 of 11 patients. All had no risk factors for AKI and, again, the events resolved. Note the 66-year-old female patient who experienced an AKI also had a major GI bleed without GI adverse event involvement and was not deemed to be drug related.

Regarding the two non-treatment-emergent cases, or as the division's briefing document refers to them as on-study events, the first patient progressed to stage 3 renal failure prior to the first insertion of ITCA 650, classifying the event clearly as pre-existing and not treatment emergent. The second patient experienced an AKI SAE just over 6 weeks after the final removal

of ITCA 650, which, per protocol, is also not a treatment-emergent case. There were no previous reported GI symptoms in these two cases.

As noted, there was one patient in Study 105 who reported a treatment-emergent AKI SAE in the ITCA 650 arm of the trial. This case was not considered study drug related, as the patient had a significant bleed that was proximal with the event, a well known cause of serious AKI. This event also resolved, and the patient completed the trial.

As Mr. Graves has shared, CDER's main reason to deny approval of ITCA 650 was a contention that no other GLP-1 products have shown a small numeric imbalance in serious AKIs in large randomized, placebo-controlled trials. Using publicly available AKI data from sponsors, the FDA, and EMA, we assessed the AKI SAEs reported for other approved GLP-1s using standardized AKI reporting criteria. Our expert assessment of these serious AKI events included using the prespecified and randomized data from GLP-1 trials, which is the gold standard for comparison to placebo.

We also used FDA's standardized AKI SAE MedDRA narrow scope search terms for each of the trials, and all reported serious AKI events in each arm of the study were identified. This includes repeat serious AKI events and hospitalizations in individual patients, which is important because when someone has a repeat case of a second AKI SAE, as the committee knows, this is unfortunately associated with a 14-fold increased risk for progression to end-stage renal disease and renal replacement therapy. Given this magnitude of severity of increased risk, it is critical to capture total events and not just the percentage of patients that had any AKI SAEs.

So now let's look at the data supporting that numeric imbalances have been observed in other GLP-1 randomized-controlled trials. To begin our review, here is a table showing imbalances for both non-serious and serious AKI events noted for ITCA 650 semaglutide and liraglutide. CDER's briefing book did not disclose the fact that there are both serious and non-serious AKI imbalances for

liraglutide and semaglutide, nor that their focus has always been on serious AKI events. Therefore, using public data from the sponsor and FDA, let's look further into the serious AKI imbalances observed first for liraglutide.

Here's data from the LEADER cardiovascular outcome trial of liraglutide, included in the sponsor's 2017 EMDAC briefing document. You can see 141 patients experienced 164 serious AKI events on drug compared to 136 patients with 153 events for placebo. As already noted, these repeat AKI events are very important clinical considerations given their association with increased risk.

Additionally, this small imbalance was also associated with 11 AKI renal-related deaths for liraglutide compared to five on placebo. The sponsor also included this table in their briefing document at that same EMDAC, showing the imbalance in AKI SAEs were noted mostly in patients with normal or mild renal impairment at baseline. This juxtaposes clearly with ITCA 650 data, where all patients with AKI SAEs had at least

mild-to-moderate pre-existing renal impairment, a known risk factor for AKI.

And here's public data for semaglutide from the SUSTAIN-6 cardiovascular outcome trial, again showing very small numeric imbalances in serious AKI events in the 0.5-milligram arm of the study. This is data provided on clinicaltrials.gov, which did not pool any AKI SAEs. SUSTAIN-6 assessed two dosing arms of semaglutide. The 0.5-milligram arm showed a clear imbalance not in favor of semaglutide, while no imbalance was noted for the 1-milligram arm.

Interestingly, and despite the sponsor's protocol that stated the two different doses were not to be pooled for analysis of safety events, CDER conducted a post hoc pooling of these two different doses in their review, which obscures the imbalance in 3 AKI SAEs deaths that were noted on the 0.5-milligram dosing arm. All of the AKI tables and plots by CDER in their briefing books pooled the 2 doses of semaglutide in SUSTAIN-6, which makes it appear as if there were no

unfavorable AKI SAEs in this CVOT; however, this is not so.

Shown on the bottom half of this page is an AKI SAE plot just like all these serious AKI plots in CDER's briefing document, which shows what CDER's plots would have and should have looked like if they followed the sponsor's prespecified protocol, which explicitly called for the two different doses to be kept separate and not pooled in all safety analyses, including AKI, which was a secondary endpoint. The point estimate and confidence levels are not in favor of the approved 0.5-milligram semaglutide dose.

This AKI imbalance data makes sense when we understand the study design of SUSTAIN-6, which started all patients on the lower 0.5-milligram dosing arm of semaglutide for the first 2 months, a time when GI AEs and AKI risk are highest. Patients randomized to 1-milligram semaglutide did not start back dose until week 9, well after the most susceptible patients would have experienced GI AEs that could lead to AKI.

Furthermore, the 1-milligram dose was found as a time- and dose-dependent favorable effect versus placebo over time that appeared to lower AKI events versus placebo during the second year of the trial. This finding only on the 1-milligram dose is now being investigated in a large confirmatory trial dedicated to assessing long-term real outcomes.

An imbalance in serious and non-serious AKI was also reported for semaglutide in the recent STEP-2 obesity trial in patients living with obesity and type 2 diabetes. For serious AKI, 0.5 percent of subjects experienced a serious AKI for both the 1-milligram and higher 2.4-milligram doses of semaglutide compared to a rate of 0.2 percent in the placebo group. There were non-serious AKI events not in favor of the study drug, as shown.

Based on this data and multiple other AKI SAEs observed on Wegovy and the trials in the NDA, it was approved with a new AKI warning that states, "Acute kidney injury has occurred in

clinical trials." An even larger serious AKI imbalance of 1.9 percent on study drug versus 0.4 percent on placebo, almost a 5-fold increased risk, was observed with semaglutide in the recently reported STEP-HF heart failure trial just published last month in the New England Journal of Medicine.

It's quite clear that there is now mounting and substantial evidence that serious AKI is a rare but real class effect with GLP-1 medicines, as noted across both multiple postmarketing reports and multiple randomized-controlled trials for GLP-1 medicines. Importantly, as I noted, AKI risk is both monitorable, manageable, and already present in the GLP-1 class labeling.

The proposed AKI warning shown here is nearly identical to the recently approved Wegovy label. It notes that AKI events have occurred in a clinical trial. The same transient GI AE pattern at dose initiation and dose escalation is seen with ITCA 650, and the proposed warning points are to monitor renal function when initiating or escalating doses in patients with renal impairment

reporting GI adverse effects.

A more expanded version of the warning also informs patients and doctors about renal impairment restrictions with exenatide and important concomitant medications, that it can increase risk of dehydration and AKI risk, as well as the importance -- and I'd like to stress this -- of proactively ensuring that patients with GI AEs stay well hydrated during dose initiation and dose escalation.

As someone involved with the discovery and assessment of this class of drugs for the last three decades, I can tell you with confidence and clarity that transient GI AEs are clearly a risk across the class that can lead to serious AKI events for any drug, based on the GLP-1 mechanism of action, with the highest risk in those with pre-existing renal impairment. But with label warnings and proactive measures, including communication and education, I believe that we can do a better job for people living with diabetes to mitigate these risks and reduce the rates of AKI.

This entirely manageable rare event should not preclude approval of ITCA 650. We have to recognize that we are currently not meeting the needs of many people with type 2 diabetes who are challenged by limitations with persistence and adherence. I believe that ITCA 650 would be an important advance for the diabetes community and provide an important, as yet not available but highly needed, option for people living with type 2 diabetes. Thanks very much, and I'll now turn the presentation over to Dr. Sager.

Applicant Presentation - Philip Sager

DR. SAGER: Thank you. My name is Philip Sager. I'm a cardiologist and adjunct professor of medicine at Stanford University. I also have a leadership role in the FDA sponsored Cardiovascular Safety Research Consortium. I have no financial interest in the outcome of today's meeting, and I'm being compensated for my time.

In regard to the issue of MACE, the FDA suggests that the prespecified primary meta-analysis showed a potentially unfavorable

hazard ratio. The meta-analysis met the FDA guidance at the time with a hazard ratio of 1.12 and an upper 95 percent confidence interval substantially less than 1.8. To come to this conclusion, the FDA performed a cross-trial comparison of ITCA 650's preapproval cardiovascular outcome study 107 with other outcome studies. The comparator trials were quite different from 107, with generally more power, smaller confidence intervals, a greater number of MACE, and different populations. In many of the CVOTs, an apparent positive effect on MACE was not evident until at least more than one year.

The median follow-up in the ITCA 650 meta-analysis was short at 1.2 years, a time period potentially too short to positively impact MACE. For example, the LEADER study had a median follow-up of 3.8 years and did not show benefits until after more than one year. Additionally, it had 7.5 times the number of MACE in Study 107. Drawing conclusions from such comparisons is problematic.

The FDA also questions ITCA 650's safety based on subgroup analyses. These subgroups are generally small, have low numbers of MACE, and thus large confidence intervals, resulting in a high type 1 error risk. While potentially hypothesis-generating, drawing conclusions from such subgroups is not appropriate. For example, cardiovascular death occurred in 51 patients, 28 versus 23, a difference of only 5 individuals that might well be due to chance.

Important to this review is the knowledge we now have of GLP-1s since ITCA 650 was first reviewed six years ago. We now know that GLP-1s, including exenatide in the almost 15,000-patient EXSCEL trial, have not been shown to cause cardiovascular harm. Thus, the biologic plausibility that ITCA 650 causes harm is very low.

The 2008 guidance specifies, a preapproval, a preliminary cardiovascular risk assessment be performed. This is met by the upper bound of the 95 percent confidence interval of 1.8 for MACE being excluded. This preapproval criteria can be

met using an outcome study combined with other phase 3 studies and a meta-analysis. This was the approach used for ITCA 650 and included three phase 3 studies, including Study 107, a preliminary short-term approval, cardiovascular outcome study designed in accordance with the FDA guidance. Once this endpoint is met, the guidance called for a larger and longer definitive post-approval outcome study.

Study 107 enrolled patients of higher cardiovascular risk with age greater than 40 years old, with either coronary disease, peripheral vascular disease, or cerebrovascular disease, but also included those considered to be at lower cardiovascular risk. This event-based study randomized patients 1 to 1 to treatment with either ITCA 650 or matching placebo.

Additionally, the primary cardiovascular safety analysis, agreed to with the FDA and defined in the statistical analysis plan, was a meta-analysis of 4-point MACE from Studies 103, 105, and 107. The FDA accepted endpoint included

cardiovascular death, non-fatal MI or stroke, or unstable angina resulting in hospital admission.

While multiple sensitivity analyses were performed, the primary focus of this presentation is on the prespecified primary meta-analysis using the intention-to-treat methodology. While most events occurred in Study 107, seven additional patients experienced MACE from the other two studies. The prespecified primary MACE meta-analysis had a hazard ratio of 1.12 and met the guidance standard with a 95 percent confidence interval of 1.51, substantially less than 1.8. The on-treatment MACE for sensitivity analyses also met the 1.8 criteria.

Importantly, the difference in MACE events between the cohorts is only 11 patients or 3.6 versus 3.4 percent, a small difference that makes it very challenging to draw conclusions regarding differences in MACE between the two cohorts. The width of the 95 percent confidence intervals is large at 0.68 and includes normality.

Looking at Study 107 alone, which was not

the prespecified primary analysis, this study also met the FDA preapproval criteria with an upper confidence interval bound of 1.63, below the 1.8 threshold. These results are again supported by the on-treatment MACE for sensitivity analyses, which also met this threshold.

One of the issues today is if a point estimate of 1.12 with an upper 95 percent confidence interval bound of 1.51 is acceptable, as shown in the meta-analysis. Here's a table from the FDA's presentation at the EMDAC meeting October 2018 that reviews the number of events and patient-years needed for 90 percent powering in preapproval cardiovascular safety analyses. 181 MACE events were reported for the meta-analysis, which aligns with the estimated point estimate and upper 95 percent confidence interval bound identified in the FDA's table. Based on powering, an upper confidence interval greater than 1.5 would be expected, as was observed in the meta-analysis. To exclude an upper bound of the 95 percent MACE confidence interval less than

1.3 would require approximately 611 MACE events, more than 3 times the number in the ITCA 650 meta-analysis. This was the approach taken in post-approval cardiovascular outcome studies.

As noted, drawing conclusions from cross-trial comparisons of pre and post-approval CVOTs are problematic. This issue is exacerbated when designs in the trials are innately different, including, one, being to rule out an unacceptable preapproval cardiovascular risk and the other to exclude a lower degree of risk, and potentially show CV benefit. Due to these design differences, preapproval studies are generally smaller with substantially fewer MACE events. The FDA specifically allows for the use of 4-point MACE in meta-analyses to increase events. These are usually of shorter duration and post-approval outcome studies.

Shown here is an example of how precision can change with a study as a function of its power when there are more MACE, a larger sample size, and longer duration. The lixisenatide preapproval

interim analysis had 263 MACE, consistent with ITCA 650's preapproval outcome data. The hazard ratio was 1.14 and the upper 95 percent confidence interval was 1.47.

In the extension of the study with longer duration and more subjects, over 800 events were observed. This is 3 times more than the initial number of events at the time of the interim analysis. With a larger number of events and power, the confidence interval width decreased by more than 50 percent and the upper 95 percent confidence interval was reduced from 1.47 to 1.17. The hazard ratio reduced from 1.14 to 1.02. Clearly, smaller studies with less power have wider confidence intervals and lower precision.

The sponsor will perform a definitive post-approval outcome study which will be discussed and agreed to with the FDA. The study would be enriched for the elderly, patients with renal dysfunction, and individuals with increased cardiovascular risk and disease. Enrollment would be sufficient to complete the trial in about

3-and-a-half years.

In summary, the primary meta-analysis achieved its objective and met the diabetes guidance preapproval criteria. It would not be expected that a study designed to exclude an upper 95 percent confidence less than 1.8 would show superiority due to the relatively few events and power.

Importantly, conclusions drawn from cross-trial comparisons of different designs, vastly different numbers of events and power, and follow-up periods, as well as patient populations, are scientifically problematic and do not replace randomized-controlled comparator trials. An adequately powered definitive study conducted post-approval is warranted.

Additionally, cardiovascular harm has not been observed across the class, including for exenatide. The exenatide EXSCEL CVOT had a strong trend to show MACE benefit; thus, a biological plausibility that ITCA 650 causes harm is very weak.

Thank you. I return the presentation to Mr. Graves.

Applicant Presentation - Kurt Graves

MR. GRAVES: Thank you, Dr. Sager.

I'll now review issue number 3 regarding device in vitro release specifications. Despite extensive clinical data that is in line with exenatide and GLP-1 products, CDRH and CDER have questioned the implants' in vitro upper- and lower-release specification limits as effective and safe for their intended use.

This premise is linked to the assertion that only ITCA 650 has an AKI imbalance in trials, which is not true. Moreover, it is not supported by the extensive clinical data from four positive, well-conducted, phase 3 trials, with efficacy and safety data in line with the GLP-1 class.

The 3-month and 6-month implants used in phase 3 met their predefined and prediscussed in vitro release specifications, and consistently released exenatide within the set upper and lower IVR limits used throughout phase 3 for the intended

implant durations. ITCA 650 implants provide a consistent osmotic delivery of exenatide that was observed throughout the clinical program.

To address the subject of PK variability, I'd like to provide some very important context about exenatide PK variability when it is injected once weekly as Bydureon. This slide is published data for exenatide, the same GLP-1 delivered in ITCA 650. Here it is delivered as a 2-milligram Bydureon injection every week.

CDER is very familiar with and has already accepted that exenatide's PK profile and Bydureon is highly variable with a 400-fold PK variability at steady state throughout this 54-week study. Despite the PK variability of Bydureon, exenatide has been shown for many years now to be safe and effective. As we can discuss during Q&A, none of the ITCA 650 PK variability -- none of it -- exceeds the known PK variability for Bydureon.

Here we show PK exposure-response for ITCA 650 versus Bydureon from public data in their

NDA. This exposure analysis versus Bydureon was suggested by the agency after our first CRL and shows HbA_{1c} on the Y-axis and normalized multiples of EC_{50} on the X-axis for both products so that we could avoid differences in PK assays used for Bydureon and ITCA 650. This is the only way to objectively assess the PK data for both programs, which used different assays. But the bottom line from this analysis is that it shows there is comparable to less PK variability with ITCA 650. This can be seen in the two bars along the bottom of the graph in red and black, which are the same width, but 95 percent of the exenatide concentrations for ITCA 650 versus only 80 percent of the concentrations for Bydureon.

CDER used some very large numbers for the IVR specifications that are not our actual IVR specifications used to test and control our devices used throughout our phase 3 program that have been clinically validated. Here I show the six IVR intervals from left to right for each of the 20-microgram per day devices and the 60-microgram

per day devices. The first interval is the startup interval before the implants reach and then maintain steady state, starting in interval 2. This startup period was the same with Viadur using the DUROS devices. After steady state is reached in interval 2, it is maintained throughout intervals 3 through 6, which cover the full 3- and 6-month durations of the implants.

The allowable variability numbers for the 3- and 6-month implants are highlighted in yellow and show the actual percentages of variability allowed in the specifications, which sets both the upper and lower limits, and is between 20 to 31 percent, not up to the 200 percent in CDER's briefing book, after the initial startup interval, which is comparable to or below the variability allowed for other previously approved implants. More importantly than comparing to other implants, these IVR upper and lower limits have been clinically validated with four successful phase 3 trials, with efficacy benefits that are undisputed by the FDA, and with a GI side effect profile and

overall safety profile that is squarely in line with GLP-1 products and labeled AKI warnings.

These weekly prespecified IVR specifications were reviewed and accepted as reasonable with the agency at the end of the phase 2 meeting when we reviewed all of our phase 1 and phase 2 data and when we used these weekly and biweekly specs throughout our entire phase 3 program, and then we even tightened them further as we gained more manufacturing data after our phase 3 program was completed.

An important measure of ITCA 650 implant delivery, consistency and reliability, is via our in vitro drug release data and manufacturing specifications. Here we show the upper and lower IVR release specification limits in the blue dotted lines over the full 3-month life of the starting dose 20-microgram per day implants. The IVR release data on the implants used in phase 3 was measured weekly and biweekly over a 3- or 6- month period, and we can see that ITCA 650 consistently delivered exenatide within the upper and lower

limits of the prespecified specifications. As with other implants on the market, the upper limit was defined for safety, which has been clinically validated, and the lower limit was defined for efficacy, which has also been clinically validated and not disputed by the agency.

As part of a supplementary data request from the FDA after our first CRL, Intarcia also developed a new testing method and completed a one-time daily IVR verification study, which is not our normal specifications, but it further demonstrated that the devices performed as designed and within prespecified acceptance criteria for the full 3-month and 6-month periods of time. Looking at the in vitro release of the 60-microgram dose over 6 months, we continue to see the same consistent delivery of the drug for the full intended use period.

Another way of assessing consistent device performance is through fasting plasma glucose reductions over time, which show meaningful and consistent results that support that the devices

are performing consistently as designed. Here we see the ITCA 650 results from the three pivotal randomized controlled Studies 103, 105, and Study 107. The first 13 weeks are the lower starting dose implants, and at week 13, the patients get their once-every-6-month implants at a 60-microgram per day dose as maintenance therapy.

As you can see, patients sustained consistent reductions in fasting plasma glucose throughout the studies with no evidence of either sporadic bolus release or early exhaustion of exenatide. If patients were getting sporadic and bolus release, the ITCA 650 implants would prematurely exhaust and would show increases in fasting plasma glucose that are not observed in our data across any of our phase 3 trials. And as Dr. Drucker presented, ITCA 650's clinical safety and GI side effect profile also supports a consistent product delivery with very low rates of GI adverse events during maintenance therapy, as you can see on this slide.

Again, if bolus release were occurring at

random, sporadic GI AEs would be observed throughout the maintenance study periods, which use multiple implants for patients very successfully with a very stable and very low rate of GI adverse events. In fact, ITCA 650's implants showed improved GI tolerability of ITCA 650 versus exenatide injections, based on a phase 2 head-to-head study we ran against the only approved exenatide injectable product on the market at the time, which was Byetta.

This study assessed the comparative GI tolerability and glucose lowering efficacy of the same daily doses of exenatide given by Byetta injections twice daily for ITCA 650 over 12 weeks. You can see that the ITCA 650 showed markedly lower GI side effects, yet better glucose lowering efficacy. This study helped us define the starting and maintenance doses of our phase 3 program, and when you look at GI AEs in much larger phase 3 trials for Byetta and the class, ITCA 650's GI profile looks and remains in line with the class.

Let me conclude our presentation now. When

considering the benefit-risk discussions, please consider the pressing needs for patients, the substantial efficacy of ITCA 650 demonstrated across four successful phase 3 trials, and the potential for ITCA 650's twice yearly maintenance dosing to offer needed benefits to patients with poor glucose control due to poor adherence with current options.

Based on the breadth of exenatide data generated, ITCA 650 has been adequately characterized. It incorporates the well-proven drug exenatide into a previously approved osmotic delivery system, a delivery system that provides consistent exposure within well-established PK variability observed for the approved exenatide products already on the market. The overall preapproval safety profile is in line with expectations for exenatide and other GLP-1s.

GI adverse events are a class risk with GLP-1s that can lead to rare but seriously AKI events for any drug in this class. AKI imbalances in randomized trials and additional postmarketing

reports all share the same biological mechanism, which is a class effect that needs to be acknowledged, labeled clearly and mitigated for the safety of patients now and moving forward, particularly as this class of drugs expands into new populations. Regarding CV safety, ITCA 650 met FDA's preapproval endpoint threshold required for approvability. This outcome should have warranted a more definitive, well-powered, and longer term post-approval CVOT study that we're committed to.

Finally, we are committed to risk mitigations post-approval. We fully support and recommend a class-labeled AKI warning for ITCA 650. ITCA 650 would be administered by trained and certified providers in any given office when educational materials can support patient understanding of GI adverse events and related risks and how to mitigate them. As noted, we are also committed to conducting a post-approval CVOT that is well powered and of longer duration to confirm both CV safety and the potential for CV benefit of ITCA 650, and we will also further

assess the short- and long-term renal outcomes.

I'd like to leave you with this, one of many letters on the docket related to this hearing. This one is from four prior American Diabetes Association presidents and 12 of the top diabetes experts that were on our external SAB, noting that AKI, in their view, is a class effect that is manageable; that CD harm is biologically implausible; and that ITCA 650's novel twice yearly dosing profile would be an important new maintenance option for many patients in the U.S. that remain uncontrolled mainly due to adherence with existing daily and weekly therapies.

Thank you very much. We'd now like to take your questions.

Clarifying Questions

DR. LOW WANG: Thank you for this presentation.

We will now proceed to clarifying questions for Intarcia Therapeutics. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by

clicking the raise-hand icon again after you've asked your question.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end your follow-up question with, "That is all for my questions," so that we can move on to the next panel member.

Now, I'd like to take the chair's prerogative and start with the first question. I think this is a question for Mr. Graves.

Could you please comment on the concern about how the variability data that you presented are determined from weekly or biweekly instead of daily IVR assessments?

MR. GRAVES: Yes. I would like to start with that. If we could go to the backup slides on daily IVR. I'd first like to start with this slide

just to anchor the committee in the way that the company has always used IVR variability limits, the upper and lower limits here in the red dotted lines.

This is the specifications that we agreed with the FDA at the end of phase 2 and that were, very importantly, used throughout our phase 3 program. This shows that our devices are delivering within that variability allowed by those IVR specifications, consistently and reliably, for the full duration of the implants. Our clinical data -- the efficacy that Dr. Drucker showed you and the safety that Dr. Drucker and Dr. Sager showed you -- are totally linked to these IVR weekly and biweekly measures that were agreed with the agency prior to phase 3.

Now, let me talk about how this relates to daily because I think there can be some confusion there, and I want to try to take that away. I'd like to go to the next slide to talk to you about what we had to do.

So after our first CRL, we were asked by the

agency if we could come up with a totally new method to look at daily release of our pumps instead of weekly or biweekly, which we used in phase 3, and this was not for new specifications, to be very clear; this was a one-time device verification study.

But we complied with the agency's requests and quickly tried to come up with a way to really look at -- we're looking here at 0.8 microliters, is what we had to try to capture precisely every 24 hours with a totally new method that we had to develop, which is not easy. And that method can introduce variability by itself because the way our pumps work, the formulation is viscous, and it comes out in little viscous beads in a consistent manner. But if you miss one of those little beads, because it's only 0.8 microliters a day, on day 1, that carries over to day 2 and looks like variability on the chart.

So we knew this, and when we set our acceptance criteria for this method, we based it off of a justification of Byetta and Bydureon PK

data. We also justified it because we knew that there was going to be inherent variability in this method.

So if I go forward and show you this next slide, what the FDA showed in their briefing book, the first half of it, was a lot of IVR data from not our specs used for phase 3, where all of our clinical data is validated, but they used this daily IVR study, with the drawbacks of the method I just explained to you, to suggest that there's wild variability with our devices.

Our devices delivered within all of our specifications, like I said, including the acceptance criteria set for this protocol. But what I want to clarify on the right-hand side of this slide is a different method that doesn't require you to try to capture these very micro amounts, the 0.8 microliters a day.

This is an experiment on the right side of the slide where we use with our implants a video camera to actually be able to capture exactly how much exenatide's coming out of our pumps over a

3-day period on a-every-5-minute basis. And when you look at it that way, it's completely linear delivery, and this is what our devices actually do do. But again, the difference between the left side of the slide and the right is the drawbacks of the method we had to try to develop for that daily amount of capture.

The last slide I'll show you, just to give you some additional data, is the same kind of data -- sorry, one last slide -- using 20 days. So this is, again, using the not daily method but looking at this even more frequently, actually. You can see the complete linear delivery of our devices does work; it's just an artifact of the method that you saw on all that daily IVR data.

So in summary, I just want to come back to the slide that was presented, and that's my last slide on this. If you put our variability in perspective, relative to Bydureon on the left -- and that's Bydureon's 400-fold PK variability that we know is safe and effective -- on the right, I'm showing you PK

variability data for ITCA 650 that we collected in phase 3, on the right there, and you can see that the PK variability with ITCA 650 and Bydureon are highly comparable.

So when you really get to how our devices work, they do deliver within their weekly and biweekly specs, they're clinically validated, and our overall variability of our devices and our PK is fully in line with exenatide that's on the market. Thank you.

DR. LOW WANG: Thank you. I do see that there are a number of questions from our panel members, so I'll start with Dr. Konstam.

DR. KONSTAM: Yes. Thanks very much, and I want to thank the sponsor for really clear presentations, and also thank Dr. Archdeacon on FDA's side also for a very clear presentation.

I want to focus my questions to Dr. Sager with regard to cardiovascular safety, and I'm going to preface it by saying that, first of all, the threshold for concern about safety is obviously a lot lower than the threshold for accepting

efficacy, so that's just a general principle, at least the way I approach safety, and probably others.

The other comment I wanted to make is about the 1.8 threshold for the upper confidence limit for cardiovascular events that is required to be below that upper threshold in order to allow approval, and then followed by a larger cardiovascular outcome trial. I just want to say, first -- first I want to say I was on the panel that recommended those criteria.

I want to point out, first, that the 1.5 that you mentioned is the upper confidence limit that you showed. I just want to mention that that means that the data have not ruled out a 50 percent increase in whatever you're looking at, and the 1.8 does not rule out up to an 80 percent increase. So those are the guard rails. But you showed the 1.5, and I never thought of that threshold as necessarily sufficient for approval of the drug. My feeling about it was that it was necessary; that it was a guidance piece that you had to fall into,

but it wasn't sort of a legalistic thing, that if you fall below that, I have to be approved.

I want to call your attention to -- now, one of the things I would say, the FDA looked at multiple different analyses, not just the primary that you showed, which I'm not sure what it consisted of. But if I look at their briefing document, pages 63 and 64, first of all, they're looking at the FREEDOM trial. They're looking at on-study analysis; they're looking at on-treatment analysis for each of the components of the MACE endpoint, and it'd be wonderful to see consistency of those findings to assure us that the 1.5 is real and it's different from the 1.8.

So let's just go down through a couple of things. On CV death, a hazard ratio of 1.22, upper confidence limit of 2.12. For on-treatment, I understand that it's a smaller number on treatment -- now, the on-treatment analysis, which I would never use as the primary analysis, nevertheless, that showed a hazard ratio of 1.5 with an upper confidence limit of 2.73. For

non-fatal MI, something very similar, on-study, a 1.33 hazard ratio, 2.18 upper confidence limit, and then the on-treatment, 1.47, 2.43. With a third component, which is non-fatal stroke, the hazard ratio sat right on 1.0. So the point estimate for the hazard ratio is consistently to the right, and I'd love to see some confirmatory data across other analyses, such as the FDA showed here, to say I'm really comfortable that the real answer is below 1.8.

DR. SAGER: Thank you for those comments and questions. As we're waiting for the slide to come, the primary prespecified analysis agreed to with the FDA was a meta-analysis using MACE 4, which has been identified as being acceptable for preapproval outcome studies by the FDA, and intention to treat, which was considered to be the gold standard. But we'll put up a slide now that looks at it in all different types of ways in terms of the on-treatment analysis.

So shown here for the meta-analysis in the upper portion and Study 107 on the bottom portion,

we had MACE 4 and MACE 3. In the meta-analysis, it was under 1.8 for all those six different analyses. For MACE 4 in 107, it was under 1.8. For the intention to treat using MACE 3 in Study 107, it was also under 1.8. And the two points that did cross 1.8 were MACE 3 using either on treatment or on treatment plus 30 days over the last two rows.

By the time we get to Study 107, MACE 3, and on treatment, we're pretty far removed from what the primary prespecified analysis was because we're now looking at Study 107 alone, we're looking at a different endpoint, and we're looking at a different analysis type. So when I look at this data from the robustness standpoint, 10 out of 12 analyses actually are below 1.8.

So I think, to me, that it being less than 1.8, Dr. Konstam, has robustness to it. And importantly, exenatide has been looked at very carefully in other studies, such as the EXSCEL trial of almost 15,000 patients, and showed no harm. So the concept that there could be biologic plausibility for harm here seems to be really low.

In comparing across other trials, which I think was alluded to, most of those trials are very different sizes, much larger, many more MACE events, and confidence intervals much more narrow. And importantly, most of the studies that have shown benefit have shown that after a year, be it LEADER, REWIND, or EXSCEL. So the follow-up period in the meta-analysis was 1.2 years, 1.4 years, so 107 alone, that's potentially a time interval also too short to start to really see benefits of this type of therapy.

DR. KONSTAM: Thank you. That's really helpful; it really is. And I'll just ask one more thing, but then I'll turn off my microphone.

I don't know what others think. I think it might be helpful if you had data from other applications at the time of approval in terms of what those data look like in terms of the point estimates for the hazard ratio, as well as the upper confidence limit, what you showed here, with a consistent point estimate that's over 1. And is that a common finding in drugs that have been

approved under this standard?

I'll thank you after asking that question.

DR. SAGER: Let's see. We need the slide that has the actual confidence intervals for the other studies. I think we can use the FDA's slide from their briefing book.

While we're waiting for this slide to come up, Dr. Konstam, I also wanted just to address the subgroup analyses, for example, cardiovascular deaths or stroke. These are subgroup analyses. The study clearly wasn't powered to look at subgroups at all, and most of those analyses -- in fact, I'd say all of them -- had very few events.

So the confidence intervals are extremely wide, and thus they're really, I think, hypothesis-generating, and conclusions really can't be drawn from them because sometimes we're comparing, again, very small numbers of patients. Cardiovascular death I think was a difference of 8 or 9 patients, for example, so it's going to have very high hazard ratios when we have maybe 50 events.

DR. KONSTAM: One just clarifying comment.

The FDA did do subgroup analyses, but these were not subgroup analyses. These were analyses in the entire population for components of the primary endpoint, just to clarify.

DR. SAGER: Right. No. I --

(Crosstalk.)

DR. KONSTAM: But your point's still taken.

DR. SAGER: Yes. It's really small with extremely wide confidence intervals.

DR. KONSTAM: Thank you.

DR. LOW WANG: I'd like to jump in. Is the slide ready to show?

DR. SAGER: I think that slide, the one Dr. Konstam wants, we'll have to get after the break.

DR. LOW WANG: Okay. Terrific.

I would like to move on. We do have several other panel members with questions, so thank you, Dr. Konstam.

Next, I'd like to call on Dr. Newman, and could you please state your name for the record and direct your question to a specific person, if you

can?

DR. NEWMAN: Connie Newman. My question is directed to the sponsor, to Mr. Graves, and this is about renal injury. I would like to know how many patients in these trials had abnormal kidney function and how was that determined at the time of randomization. In other words, I'm trying to assess whether people with kidney injury were studied adequately in these trials.

Also, if I may, I wanted to also ask how the kidney injury events were adjudicated to be serious, because there were many more acute kidney injury events, and was there a specific process, a blinded process, for adjudicating these events as serious? Thank you.

MR. GRAVES: Thank you.

Can we go to core deck slide 10 for a second, just to frame the data that I talked about? The main data, and the first time these imbalances and serious AKI events emerged, publicly at least, was in 2017, when we had the first cardiovascular outcome studies that reported out, and three of

them reported out, the LEADER, Study 107, and SUSTAIN-6, as you can see on the left side of this slide.

In each of those studies, roughly 70-to-75 percent of patients, including our study -- our study was 70 percent -- had baseline renal impairment defined as an eGFR under 90. So we had mild-to-moderate renal impairment patients in ours, and the reason for that is exenatide is renal cleared, so it's contraindicated in people with stage 3b renal impairment or worse, so we followed the label for exenatide in our study, but 70 percent of the patients had underlying renal impairment. We did not see any -- not a single case -- of serious AKI in normal renal function patients in our entire NDA. The 11 versus 4 events in our study were in patients that had mild or moderate renal impairment.

On LEADER and SUSTAIN-6 -- and I can say this for both of them -- the imbalances in their AKIs were not just reserved to people with renal impairment. Both of those studies had numeric

imbalances and serious AKI events in people that had normal healthy renal function as a component of their imbalances.

So that's the data that's at least available publicly that I can share with you on that question, and our definition of serious AKI is the same MedDRA definition that the FDA asked all sponsors to use, so we're not interpreting data in a different way. We all use standard MedDRA definition versus version 18, narrow scope, to define those serious AKI events, so you're looking at apples to apples across each of these studies.

DR. NEWMAN: Thank you. Just one more question related to kidney injury at baseline. How many subjects had GFR estimated to be below 60? Do you have that data?

MR. GRAVES: In each of these studies?

DR. NEWMAN: No, in all of them together, or at least for FREEDOM, if you know that, the FREEDOM trial.

MR. GRAVES: Right. Because of ours, it was a small percentage. I can get back to you after

the break on the exact percentage, but it was small, again, because under 60 for exenatide is not really a commonplace that exenatide, even the approved version of it, is used because of the renal restrictions of a renally cleared GLP-1.

DR. NEWMAN: Thank you.

I have no further questions at this time.

DR. LOW WANG: Thank you.

Next, I'd like to call on Dr. Munir, and remember to please state your name for the record.

DR. MUNIR: Kashif Munir. My question actually initially was going to be about the IVR that Dr. Low Wang initially mentioned, but I think the big advantage to this device, obviously, is the 6-month and elimination of adherence issues. But if you truly are getting very low or no drug delivery on certain days, that would be almost equivalent to nonadherence. And I know looking at correlate markers like glycemic variability have too many factors that might play in, so that might not be a good correlate either.

But I guess my question is, looking at the

6 months, are there people that the drug might run out before 6 months also, just looking at adherence? I mean, I guess the only way to know is that the glucose levels might start to rise. Is there any way to tell if that was happening and what percentage that might happen in?

MR. GRAVES: That's a great question. Thank you. I'd like to get the slide that I presented which addresses your question. This is a fasting plasma glucose slide for each of our phase 3 studies, so this is Study 103, 105, and 107. These are three pivotal studies, and you can see that both the 3-month devices for the first 13 weeks, those are our starter devices. Those are the 3-month devices. After 13 weeks, all the data you're seeing here are 6-month devices for maintenance therapy, and you're not seeing any upswings in fasting plasma glucose, which means the devices are performing as they're designed for the full duration, providing that efficacy.

DR. MUNIR: Yes. I guess this is just the population as a whole, right? I think there's

individual variability, though. So were there any patients where you did see an abrupt increase maybe at the 5-month mark or something like that?

MR. GRAVES: Well, let me try to address that differently. The short answer to that is, no, I'm not aware of that, but let me show the 60-microgram IVR data again just to show.

If you want to look just at, pure, are the devices delivering for the full duration, the best slide to look at is this slide right here. Before we ever release products to use in clinical trials or commercially, every lot has to pass these specifications so that we know they're delivering within their specifications for the full duration of the implants.

This is 6-month implants, and every data point there in red -- between the upper limit is the dotted red line and the lower limit is the dotted red line as well -- those are the upper and lower limits of IVR. And you can see here thousands and thousands of data points that are all delivering within those specifications for the full

6-month period of time, and this is showing you the devices are working reliably and consistently. They're not declining below there and not going to be giving efficacy. And that's why we've seen robust and consistent efficacy in every one of our phase 3 studies.

DR. MUNIR: Thank you.

MR. GRAVES: Thank you.

DR. LOW WANG: Thank you.

I'd like to now call on Dr. Brittain. Please remember to state your name for the record.

DR. BRITTAIN: Yes. This is Erica Brittain, and I have a question about slide CO-47.

MR. GRAVES: Can we have CO-47, please?

DR. BRITTAIN: Right. Thank you. And again, I agree that it was a nice presentation, very clear. Thank you for that.

MR. GRAVES: Thank you.

DR. BRITTAIN: So I have a few questions about this. I want to make sure I understand if when you're presenting us information about these other trials, are we seeing all of them or we're

just seeing the ones where there was a difference? I wasn't sure if there was a systematic, maybe not a full-blown meta-analysis. But that would be one of my questions. Did you consider doing a meta-analysis so you could look at the magnitude of the effect in the other trials versus this trial? That's one question.

Also, the event rates are lower in your trial. Is that because it's a shorter follow-up time?

MR. GRAVES: Let me address both of those. The event rates, they're actually low in all these trials. The numeric difference, anyways, is low. There are different patient populations in each of these studies, and that's why I think we have to be really careful about cross-trial comparisons because they're different durations, they're different patient populations. Some of these studies have more moderate severe patients than were in our study.

But if you look at this just as, are we seeing a consistent signal of a small numeric

imbalance in AKI across studies, that's the real, I think, central point of the data that we're presenting. It's a consistent signal, where we're seeing these small not significantly different for any of these drugs. So there are small differences, but it's a class effect, and we know it's caused by GI side effects and dehydration. That's, in fact, noted in the FDA warnings.

On your other question, as a sponsor, we obviously don't have patient-level data for all of the studies. What we've done with our external scientific advisory board -- Dr. Drucker and the other 12 endocrinologists on our external scientific advisory board -- we've looked at all the published literature around serious AKI events, where we do have public reliable sources, many times from the FDA themselves, many times from the EMA reviews, and the third source was sponsor data that was, in fact, disclosed at the EMDAC.

So if you look at the liraglutide data, that's data from the sponsor's EMDAC briefing in June of 2017. It's not an interpretation of

Intarcia; it's the facts in that briefing book. And for semaglutide, the serious AKI imbalance there is the sponsor's publication of those serious AKI events and the imbalance, which didn't happen till well after approval, but it was finally disclosed, and that imbalance was first seen when the sponsor put their data on the clinicaltrials.gov site multiple months after the EMDAC and the approval happened. That's the first time I'm aware, at least, that data became available, but it's directly from the sponsor on classic MedDRA standard definitions version 18 just like we used.

DR. BRITTAIN: Okay. Just a quick comment about the MACE, I think you made an important point about some of these other trials having a longer follow-up and the treatment effect could change as time goes on.

Can you show us -- maybe not now but perhaps after the break -- what your survival curves look like versus public survival curves from the other trials?

MR. GRAVES: Sure. I can show you other trials, and then I'll have Dr. Sager come up and comment on ours. Let me just show you, this is a few of the studies -- as Dr. Sager said, doing cross-trial comparisons against these studies are fraught with risks because we're talking about studies that have 2-to-3 times longer duration than ours, and sometimes, in the EXSCEL study, up to 11 times more cardiovascular events than were in our preapproval study. But I think one of the central points of the difference between a preapproval study, which is never designed to even look for benefit, versus these post-approval studies, is you really don't start to see the Kaplan-Meier curve separate, demonstrating the potential for benefit, until after 12 months, and then the longer the trials go, that's where you're starting to see the benefit be realized more and more over time.

Dr. Sager, would you like to talk about our curve?

DR. SAGER: Sure. Philip Sager. This is

the meta-analysis primary CV outcome data. The median time follow-up was 1.2 years, so it's much shorter than the other trials, and you can see there's a relative degree of overlap. Again, the hazard ratio was 1.12.

DR. BRITTAIN: And you don't have confidence bands for this figure.

DR. SAGER: No, but they would certainly wildly overlap.

DR. BRITTAIN: Right. I'm assuming they're getting very big as time goes on. Okay. Alright. Thank you very much.

MR. GRAVES: Thank you.

DR. LOW WANG: Before I call on Dr. Everett, I just wanted to make a comment on slide CO-47. Dr. Brittain had a question about whether or not all of the data were being shown. I did want to make a comment that for the SUSTAIN-6 trial, the acute renal failure instances were reported in the original publication in the New England Journal, and these data that we're looking at here are only for the 0.5-milligram dosing arm. So I think that

question that Dr. Brittain had about whether or not all of the data were being shown, I think that the 1-milligram is not being shown here, so I think that's just a quick point to make.

I'd like to call on Dr. Everett. Please state your name for the record.

DR. EVERETT: Hi. It's Dr. Brendan Everett from the Brigham and Women's Hospital in Boston. If you could actually pull up CO-47 again; that was specifically where my comment was.

MR. GRAVES: Sure.

DR. EVERETT: We've heard, I think, from you and also from Dr. Sager that we should hesitate to make cross-trial comparisons when it comes to efficacy, or at least with effective cardiovascular safety or lack of evidence of harm, but here you've made the case, and I think a strong part of your your case, that there is an acute kidney injury risk that is consistent across the class of GLP-1s.

So I was wondering, because I think this slide, as Dr. Low Wang just intimated, does not show all the data. I've just looked up the

inclusion criteria for the SUSTAIN-6 CVOT, and I'd like you to compare and contrast those with the inclusion criteria with respect to kidney function for your cardiovascular outcome trial, FREEDOM, where I think the bulk of the AKI events come for your product; correct?

MR. GRAVES: So all of our serious 11 events on drug and actually the four on placebo, too, were all in patients with mild-to-moderate renal impairment in our study.

DR. EVERETT: So the semaglutide trial that you've cited here actually selected 4 patients with CKD class 3 or higher. They actually actively recruited patients with kidney disease and stratified their randomization based on a GFR above or below 30, which is actually CKD 4 basically; right?

MR. GRAVES: Right. They had a small percentage of those in there, and that's what I mentioned earlier in one of my comments. That's why you have to be careful about cross-trial comparisons. Our point in this data is that

there's a signal --

(Crosstalk.)

DR. EVERETT: Okay. But I guess what I would ask you is if you see a signal of acute kidney injury, where the recruitment goal is to include patients with a high proportion of chronic kidney disease, in fact CKD 4 and 5 even, and that then the rate of ACE inhibitor and ARB use is 96 percent, as compared to a product where it's actually not supposed to be used when the GFR is less than 60 -- did I hear you say that earlier? Is my understanding correct?

MR. GRAVES: Under 45.

DR. EVERETT: Under 45. So if --

MR. GRAVES: That's the current label, yes.

DR. EVERETT: Yes. I just looked at the Nature Medicine paper, and about 75 percent of patients are on ACE inhibitors and ARBs, so it's a little bit apples and oranges, wouldn't you say, that an AKI signal seen in SUSTAIN-6 CVOT is the same as a patient population, where the baseline renal function is better and the baseline use of

ACE inhibitors and ARBs is about 20 percent lower?

MR. GRAVES: Let me try to put this all in perspective, again, with data, actually. If I could have the slide for SUSTAIN-6; and we presented a part of this earlier. Dr. Drucker did show the 0.5-milligram and the 1-milligram data. He showed the whole data in his main presentation, but I want to show you in SUSTAIN-6 that what we're looking at here with normal renal function patients is where the imbalance was actually seen, and you're not seeing it just in mild, and moderate, and severe patients, so the actual data, when you look at the the FDA's review -- and I'm just going to show you this slide -- they have a table in the FDA review that looks at AKIs by mild, moderate, and severe on end stage, to your point it was a small number, but it was there.

The question was, from the review document, they didn't show the normal renal function patients, which were around 30 percent of the patients in that study, but you can impute the data from all the numbers in there, and that's going to

be this slide, which breaks out -- this is SUSTAIN-6 data from the FDA review, all numbers from them, not us, and you can see that the imbalance is actually in patients with mild renal impairment and normal renal function, 11 events on the 0.5 milligram versus 4 on the placebo.

So I don't want people to walk away with the idea that these imbalances are coming from more severe patients. The imbalances in this trial and SUSTAIN-6 -- and I want to show one more. If I can see the LEADER renal function AKI imbalance, this is also data from FDA's briefing book back in June of 2017 on LEADER, and you can see here the same kind of data. And this, again, is in FDA table 57, normal, mild, moderate, and severe renal impairment. The imbalance that's seen on liraglutide, which was 164 events versus 153 in total, is actually coming from people, part of it, with normal renal function and mild renal impairment.

Now, our population would overlap with the left side of this slide. We did not see any, not a

single case, of AKI SAE in normal renal function in our entire NDA. We only saw it in patients with mild and moderate renal impairment. I don't want to make any conclusions on that. I just want to show you the facts of the data that's out there, and I think, hopefully, that gives you a perspective about where these events are happening.

DR. EVERETT: I appreciate the response. Thank you. I think we can talk about this more maybe in the open discussion, so I'll close there. Thanks, Dr. Low Wang.

MR. GRAVES: Thank you.

DR. LOW WANG: Thank you.

I'd like to next call on Dr. Cooke. Please state your name for the record.

DR. COOKE: Thank you. This is David Cooke, if I can get my camera on. While I'm trying to get my camera on, a pretty straightforward question.

Can you pull up slide 72?

MR. GRAVES: Sure.

DR. COOKE: Help to me to understand, because this data is confusing me a little bit --

MR. GRAVES: Sure.

DR. COOKE: -- why are the data for the 3rd, 4th, 5th, and 6th intervals identical?

MR. GRAVES: Because the pumps are basically at steady state, and just a little, very brief context. When we acquired the DUROS technology that was used for the oncology product, they had three intervals, the startup, a second one, and the third one. There was no 4, 5, and 6. So on their devices, there was no regulatory requirement to have a spec through the full through life of their implants.

The FDA asked us to add one, and we did, which is a challenge for implants. If you look at a lot of other implants that are on the market for birth control, and like Supprelin LA, the consistent delivery in those tend to fall off over time, and then birth control really falls off over time. But we were able to set reliable specs that were maintained the entire through-life of the pump. And when I show you the data -- this data here just to connect the dots for

everybody -- that's showing those consistent same specs you just asked about across 3, 4, 5, and 6 for the full through-life of the devices.

DR. COOKE: Yes. But again, back to the prior slide, it just seems really unusual that the numbers are exactly the same. The percent variability to the 10th of a percentile is the same for those four intervals. I'm just surprised by that. Do you have any [inaudible] --

(Crosstalk.)

MR. GRAVES: I appreciate your question, and the honest answer is it's because these things deliver linearly, like I showed earlier in the presentation, and it's a linear release of the drug the entire time of the intended duration, and that's how we control it.

DR. COOKE: Well, if look at your next slide, the data towards the end is a little bit different than the data towards the beginning.

MR. GRAVES: Which one was that?

DR. COOKE: The second slide you were just showing. There isn't tail [indiscernible]. I

mean, the thing at 168 days doesn't look identical to the one at 56 days. So I'm just surprised that the averages are the same, but let me move down to the next question.

MR. GRAVES: Sure.

DR. COOKE: I'm just interested. In a situation of dehydration, do you know what the impact of that would be on drug release from this device, either modeling from an in vitro standpoint or ideally pharmacokinetic data in a patient both in terms of drug release during dehydration? And maybe even more importantly, whether there's a change in that drug release after correction of dehydration.

MR. GRAVES: So the best way to answer your question is, all we know for our product -- let me start with ours -- is that there are two time windows when you're going to see GI side effects. It's at dose initiation and when we switch and go to the 6-month devices at week 13. Those two periods -- and I can just put the chart up, if I can show you.

Can I have the chart of GI side effects from the main deck? This shows you the data that I'm referring to. This is 4,156 patients in our cardiovascular outcomes study, half of them here illustrated on drug. So you can see that -- and this is true for all the other exenatide products and GLP-1 products as well -- where you get GI side effects, we know with this class of drugs, is when you initiate them, and then it goes down pretty quickly on ours; you can see even before week 13. And then when you take the starting implant out and you put a new one in, you get an additional transient increase in the subset of patients, and then it goes down and stays down below 2 percent the entire time. Those blue arrows at the bottom there are where we changed implants multiple times for maintenance therapy, but you can see that -- as it is, and it's not just our drug -- GI tolerance develops after dose initiation and dose escalation, and the side effect rate is very low.

So what matters for AKI, for our drug and the other ones, since they all do the same thing

and it's the same mechanism, is to make sure we monitor those GI side effects that we know are going to happen in a subset of patients with all these drugs in those two dosing windows. That's where it matters. That's where a hundred percent of our imbalance was. We didn't have an imbalance in AKI events after dose escalation. It's right in those two windows, and we think that's monitorable.

We can tell people you have to be aware of this, you have to watch it, you have to make sure you stay hydrated, and if you start to get dehydrated, we would instruct them to call their doctor and have a discussion about looking at their meds, including the potential for ITCA 650 to be removed, if needed.

DR. COOKE: Is there any thoughts on what would happen during dehydration with your device, whether that changes the drug delivery?

MR. GRAVES: No, that wouldn't change the drug delivery at all. You'd basically have to be a mummy not to have enough body fluid to keep it working the way it always does.

DR. COOKE: Okay. Thank you.

MR. GRAVES: You're welcome.

DR. LOW WANG: So we are at time, but we're going to take a few more minutes for another couple questions, and I'll ask that both the questions and the responses be concise.

So I'd like to next call on Dr. Burman. Please state your name for the record.

DR. BURMAN: Thank you. Ken Burman, and this is for anyone, and it's a very straightforward question. Is there a specific creatinine clearance that you would recommend for the package insert, where you don't initiate the product or you remove the product? You mentioned CKD stage 3, which is a wide range of creatinine clearance, and most of the other agents on the market have a specific creatinine clearance. Do you have any recommendations or thoughts on that?

MR. GRAVES: Yes, we do. Thank you for that question. Bydureon's label limits the use of the product in patients under eGFR of 45. And in our last NDA submission, since our PK profile looks

just like Bydureon in the data I showed you, we also recommended in that NDA submission that we limit our label to not be used in patients under 45 as well, and that's our current recommendation based on knowing the Bydureon data, based on knowing our PK is the same. That's the recommendation.

DR. BURMAN: And then real quickly, does that also mean that if the creatinine clearance was less than 45, you should take out the the device?

MR. GRAVES: I think if the patient is not having any GI side effects, there wouldn't necessarily be a need for that. Where you have to worry about patients with eGFR under 45 is when you're initiating therapy. Those patients, because exenatide is renally cleared, like lixisenatide and other GLP-1s, you want to be careful when you initiate in people under 45 because the drug levels will go up, and there's a chance that you could get more GI side effects, and we don't want to see that in those at-risk patients.

DR. BURMAN: Thank you.

MR. GRAVES: Thank you.

DR. LOW WANG: Our last question before the break, I'd like to call on Dr. Kalyani.

DR. KALYANI: Thanks. Rita Kalyani. My question relates to -- two questions -- slide CO-30, and perhaps a question for Dr. Drucker. We heard a lot about IVR variability, but as an endocrinologist and clinician, I look at glycemic variability, and I appreciate the A1C efficacy and reduction, but I wonder if you could provide more details on the hypoglycemia of 9 percent, when that occurred, what definitions you used for that, did anyone need assistance? And then, did all your participants have CGMs to detect those or how were they detecting?

MR. GRAVES: Dr. Drucker?

MR. GRAVES: So I can start on the hypoglycemia, and then have Dr. Drucker come in.

As you can see in the footnote on this slide, we did not see issues with hypoglycemia in our studies. The only time we did see it -- let me say it differently. The only time we saw it was in

our cardiovascular outcome study when it was being used in combination with insulin or sulfonylurea, which is the same for the class, and if you do see hypoglycemia, it's usually in that context. We did not see any hypoglycemia when insulin and sulfonylureas were not being used with our product in the program, and that's again very similar with exenatide data and other GLP-1 data.

And I can have --

(Crosstalk.)

DR. KALYANI: And how was that --

MR. GRAVES: -- Dr. Drucker address the rest.

Oh, I forgot to mention, we did not have CGMs used in these trials, given when they were conducted. If we were doing them today, we would, and we will going forward, but it wasn't done back then. Thank you.

DR. DRUCKER: Those are the points I was going to make, that the context of these trials historically was years ago, and it would be great to have that data today.

DR. KALYANI: And how was hypoglycemia defined in this row here?

MR. GRAVES: Let me get back to you on the break on that one. I will have to go look exactly for the definition from the protocol.

DR. KALYANI: Okay. Thanks. I have one other follow-up question. Percent glycemic rescue was reported I saw for 103 and 105 -- I didn't see it in the FREEDOM trial -- at 17 percent and 15 percent. Could you talk about how early in the trial that occurred, how high the random glucose went -- I know you provided a slide on average fasting glucose -- and how does this compare to other trials for other GLP-1s?

MR. GRAVES: If it's ok for you, because you just asked some comparative ones, too, let me collect that during break, and I'll get back to you on that. We'll be able to.

DR. KALYANI: Sure. Thank you.

MR. GRAVES: Thank you.

DR. LOW WANG: Thank you.

We do have a few more panel members with

questions, so we'll try to get to those later on today.

So now we'll take a quick 10-minute break until 11:30 Eastern Time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. We'll resume at 11:30 Eastern Time.

(Whereupon, at 11:20 a.m., a recess was taken, and meeting resumed at 11:30 a.m.)

DR. LOW WANG: Welcome back.

We will now proceed with FDA's presentations, starting with Dr. David Wolloscheck.

FDA Presentation - David Wolloscheck

DR. WOLLOSCHECK: Hello, everyone. My name is David Wolloscheck, and I'm the assistant director for the General Hospital Devices team in the Division of Drug Delivery, General Hospital Devices, and Human Factors in CDRH. I will present on the device review conclusions for the ITCA 650 review.

Before I start to discuss our findings, I

would like to provide a brief overview of drug delivery devices, particularly when they are part of drug-device or biologic device combination products. Drug delivery devices are intended to deliver the intended dose of a specified drug. There are a number of different devices that may be used to deliver a drug, and some common ones are prefilled syringes; pen injectors; autoinjectors; on-body infusion devices; and large volume infusion pumps. When selecting a drug delivery system, it is important to ensure that the chosen device is suitable for the specific drug and patient population.

Some important considerations are to ensure that device performance is adequate to achieve the intended therapeutic effect. Another important consideration is to ensure that the device is compatible with the intended drug. For example, fluid characteristics such as viscosity can have a significant impact on device performance, and it's important to ensure that the device performs adequately with the intended drug.

As most of you will know, accurately dispensing a viscous fluid such as the saturated glucose or glycerol solution with a pipette or syringe is much more challenging compared to dispensing water. In addition, it is important that the device design meets the patient or user need. This would include an assessment of device characteristics such as usability and forces required to operate the device.

In contrast to injection products, infusion products are intended to deliver a drug at a specified rate. For these devices, it is important to ensure that the infusion rate accuracy is clinically acceptable for the specific drug. Most of the time, these devices can deliver drug at different flow rates with an accuracy of plus-minus 5 to 15 percent. Because these devices deliver drug over time as opposed to a one-time injection, interruptions or malfunctions are typically communicated to the user via alarms. Hence, alarms are common for issues like fluid path occlusions, air in line, or free flow of drug.

With that in mind, the ITCA 650 product is a drug-device combination product that consists of an exenatide drug suspension and an implantable osmotic pump referred to as DUROS. The device uses a pumping mechanism controlled by osmotic pressure to deliver exenatide. After implantation, interstitial fluid diffuses through the semi-permeable membrane and hydrates a salt tablet. This causes the salt to expand, which exerts a force onto the piston, leading to release of drug. The diffusion moderator consists of an array of hollow cylinders that is intended to control the drug delivery.

The product is proposed in two different presentations, a 3-month, 20-microgram per day implant and a 6-month, 60-microgram per day implant that differ in the amount of exenatide loaded into the device. While the particular device has previously been approved for use with leuprolide, it is important to note that beyond the clinical differences between exenatide and leuprolide, the proposed exenatide suspension is more viscous

compared to the approved leuprolide solution. As mentioned previously, viscosity can have a significant impact on the drug delivery performance of a device.

It is also important to note that the DUROS device does not have a means to communicate the drug delivery status or any issues with drug delivery to the user. Hence, users are not being made aware of device malfunction and issues with the delivery of drug can only be recognized by the onset of symptoms associated with over- or under-delivery, and only if these symptoms would be attributed to the implant.

The device is intended to consistently deliver 20 or 60 micrograms per day to the patient over the duration of use. As such, the most important device performance attribute is drug release accuracy. To assess the device performance, the applicant developed an in vitro drug release assay. For this assay, the ends of the device are either placed into a saline solution or a release medium. This initiates the drug

delivery from the device, and samples are taken at specified time intervals. Exenatide is then quantified using high-performance liquid chromatography or HPLC.

The in vitro release data was collected in a controlled environment which represents idealized conditions to measure drug release from the device. Initially, in vitro release data was reported either weekly for the 20-microgram per day product or biweekly for the 60-microgram per day product. You can see an example plot of the in vitro release testing on the right, with the amount of drug released in micrograms on the Y-axis and the time and days on the X-axis. This particular graph was taken from the applicant's backgrounder.

It is important to note that this graph is generated from data collected weekly and adjusted to a daily delivery rate. In addition, the line represents an average of the tested devices, which would suggest a relatively steady release of drug. However, measuring drug release every 14 days does not represent a clinically meaningful delivery

interval and can mask variable day-to-day drug delivery. This is particularly the case given the 2-to-4 hour half-life of exenatide in the body.

To illustrate this point, I created the graph on the right that depicts in vitro release rates of three hypothetical devices. Each of these three devices delivers 840 micrograms of drug over the 14-day period. While hypothetical device number 1, depicted by the blue line, evenly delivers 60 micrograms per day over the 2-week period, device number 2 and number 3, depicted by the red and green lines, respectively, has a much more variable delivery profile, with periods of high and low drug delivery. As all three hypothetical devices deliver 840 micrograms over 2 weeks, they would all show the same biweekly delivery, and this observed variation would be masked due to under-sampling.

To better assess the drug delivery profile of ITCA 650, FDA requested daily sampling based on clinical use and feasibility. Daily in vitro release data was provided in the NDA resubmission.

The previously described measurement methodology was adopted for daily sampling and new acceptance criteria were provided for the study, which are listed in this table.

To provide context, I wanted to briefly mention common dose accuracy specifications for other drug delivery devices. For example, injection devices such as pen and autoinjectors used for other approved exenatide products typically have an accuracy of plus-minus 5 percent of the intended dose based on ISO 11608 Part 1. Infusion devices typically have an infusion rate accuracy of plus-minus 5 to 15 percent. Generally, those accuracy requirements should be based on clinical need and ensure that devices that are delivering at the extremes of the specifications are still safe and effective.

As you can see in the table, the proposed acceptance criteria for daily in vitro release are wide and would allow for significant variability in the delivery of drug. For example, in the first 4 weeks, the device will be allowed to deliver

between 2 and 120 micrograms per day, which represents between 3.3 and 200 percent of the intended dose.

As a better visual representation of these acceptance criteria, the graph on the right depicts the delivery profile of three hypothetical devices during the steady-state phase, which is described as starting from week 5 until the end of use. In this phase, the proposed acceptance criteria would allow delivery of between 25 and 110 micrograms per day. Each of the three lines are representative of the delivery profile of a device that would pass the proposed acceptance criteria.

The following two slides show examples of the daily in vitro release data provided by the applicant for the 60-microgram per day presentation. The daily delivery study for these devices was broken up into two groups. Group B tested delivery was between 0 and 112 days and Group C between 112 and 182 days. Each of these groups consisted of 12 devices.

The figure on the slide shows the results of

the daily in vitro release testing of the 60-microgram per day presentation of ITCA 650 from day 0 to 112. Each of the four panels depicts the delivery profile of one individual device over this time period with time in days on the X-axis and delivered exenatide on the Y axis. Daily sampling was not performed throughout this entire study, which is why there are periods without data in these graphs.

The data shows that day-to-day drug release is more variable compared to the weekly average data. Daily delivery ranged from 0 micrograms per day up to 103 micrograms per day. There was some variance observed between devices where the variability of drug delivery was more pronounced in some than others. All tested devices shared similar trends at initiation of the study, where there was an initial low delivery of drugs followed by a period of higher drug delivery. After this period, delivery remained variable throughout the study. It is important to note that there are observed deviations from the proposed acceptance

criteria. For example, unit 8B depicted on the top right panel delivered 1 microgram per day of exenatide on day 4.

This figure shows examples of the Group C devices, which were tested between days 112 and 182. As can be seen from these examples, variable daily delivery persisted throughout the 6-month use period of the device. Outside of the initial 1 to 3 weeks, devices from this test group showed the highest day-to-day variability, with unit 6C displaying the greatest post-startup phase, day-to-day variability among the tested 6-microgram per day devices.

I wanted to briefly touch on the daily IVR specifications and the applicant's figure 33 and 34 in their briefing document, where they state that FDA has misinterpreted the daily IVR specifications. To orient you, this slide shows figure 34 from the applicant's backgrounder. The left table shows the acceptance criteria that were provided in the daily IVR study reports in the NDA. The table on the right shows the applicant's daily

IVR specifications that were first proposed in the applicant's backgrounder documents for this advisory committee meeting. What appears to be tighter daily IVR specifications provided in the applicant's backgrounder represents the weekly and biweekly specifications listed in the NDA but modified to adjust them for daily delivery.

To assess the device performance when applying these newly proposed specifications, we analyzed the daily IVR data again. This table shows the number of 60-microgram per day devices that would pass these proposed specifications. In total, we counted 200 out-of-specification events with none of the devices performing within these specifications over the first 14 days. At best, 7 out of the 12 devices performed within these specifications between days 70 and 84 and 126 to 140.

While we disagree that FDA misinterpreted the acceptance criteria for the daily IVR study, the provided daily specifications by the applicant do not address FDA concerns of observed device

failures in the daily IVR study and, in fact, these newly proposed specifications would lead to more out-of-specification events in the daily IVR study.

In addition to the proposed device performance, specifications, and variable day-to-day drug delivery, we also have questions about how the applicant characterizes device failure modes and the resulting failure rates. Specifically, according to the applicant's analysis approach, devices that demonstrate an out-of-specification event are not automatically considered a device failure.

Generally, a device that performs outside clinically supported specifications should be assessed as a failure. In contrast, the applicant applies a different set of criteria when assessing a device failure. For example, the failure mode inconsistent formulation delivery is defined as a device that delivers equal to or greater than 50 percent of the target weekly IVR rate in three separate instances. This methodology of characterizing device failures can significantly

underestimate the number of devices that would experience this failure mode and it is not clear how the applicant's method for analyzing their data adequately captures clinically meaningful device failure events. As previously discussed, there are instances in the small group of devices tested where devices did not meet the proposed acceptance criteria; therefore, the actual failure rates of the device are higher than what is claimed by the applicant.

To summarize, the day-to-day drug delivery is highly variable throughout the intended use period under idealized in vitro conditions. Weekly or biweekly IVR sampling rates mask the inconsistent daily IVR performance. The proposed acceptance criteria allow for significant variability and lack clinical justification, and device failures are more frequent than is typical for drug delivery devices, and users would not be able to detect device failures.

This concludes our device review findings. I will pass it to Dr. Edwin Chow to discuss the

clinical pharmacology findings.

FDA Presentation - Edwin Chow

DR. CHOW: Good morning. My name is Edwin Chow, the clinical pharmacology team leader at the Office of Clinical Pharmacology. I will be presenting our assessments in the in vivo performance of ITCA 650.

The interpretation of the in vivo pharmacokinetic data is critical in the understanding of the drug release performance of ITCA 650. In this table, I have listed the main methodologies that were used by the applicant and CDER on the in vivo performance assessment of ITCA 650. In the following slide, I will provide CDER's insight on the use of these methodologies by the applicant, followed by CDER's interpretation of the in vivo PK data of ITCA 650.

Exposure-response analysis is a traditional method used to understand the relationship between exposure and efficacy and safety. The applicant has used a PK/PD model to describe the exposure-response relationship of A1C lowering

effect between ITCA 650 and Bydureon. The applicant estimated the EC_{50} value, which is the concentration required to obtain 50 percent response between the two products, to be overlapping in range. The applicant claims that the data support their argument that the two products have similar efficacy; however, there are a few limitations for this assessment.

First, average concentrations were used for the exposure-response analysis and did not provide information on the event of sudden excursion in drug concentration to pharmacodynamic response. Second, the A1C response, which takes about a minimum of 8 to 12 weeks to alter, is not a sensitive metric to capture the impact of sudden excursion in concentration. Third, the primary concern in the phase 3 study, 103, is not efficacy, but the uncertainty in the prediction of adverse events. In addition, there is no established exposure-response model to evaluate safety, specifically AKI and MACE.

Thus, exposure-response analysis using

average drug concentration will not provide us critical information on the individual level to interpret any sudden excursion in drug concentration by the drug release performance of ITCA 650.

In addition to exposure-response analysis, the applicant used mean concentration data from concentration time profile to support that the ITCA 650 has consistent drug delivery similar to other exenatide products such as Bydureon. The figure here shows you the mean exenatide concentration time profile of Bydureon and ITCA 650. The Y-axis is plasma exenatide concentration and the X-axis is the PK collection time in days of the particular week. The dots and bars represent the mean and standard deviation.

We note that we cannot make a head-to-head comparison on the drug concentration between the two products, as different PK assays were used; however, these parts suggest that both products appear to provide consistent drug delivery with similar PK variability between days, but there are

limitations in using mean drug concentration time profile to visualize the in vivo performance of these products.

First, the mean values do not provide you the information on the day-to-day fluctuation within the same individual subjects. Second, the observed fluctuation is the total variability, which is a combination of between-subject and within-subject variability. To assess the variability of daily drug release by ITCA 650, I will provide a brief introductory on the key concept of between-subject and within-subject variability and how they divide.

This slide illustrates the basic concept of between-subject and within-subject variability. The left figure shows you a hypothetical concentration time profile of three individual subjects with varying levels of drug concentration over time. Intrinsic factors such as body weight or organ function may contribute to the differences in drug concentration. The between-subject variability is an estimate based on the variation

of the mean drug concentration of all subjects, as highlighted by the black arrow. On the right figure, fluctuation of drug concentration over time can occur within the same subjects.

Formulation factors such as how the drug is released on the particular day may affect the drug absorption and exposure. The variation in drug exposure on different days within the same subjects is what we call within-subject variability, as highlighted by the small black arrows. Thus, what this tells us is that in order to assess sudden excursion in drug concentration relating to the in vivo performance by a continuous drug release product, we need to evaluate the individual concentration time profile as well as the within-subject variability. In addition, the within-subject variability should be assessed between shorter time intervals in order to have a better understanding of any sudden excursion in drug concentration related to the product performance.

The ITCA 650 program has very limited

studies with robust PK information available to assess the individual concentration time profile, as well as to assess the estimation of PK variability; however, we are able to use the PK data from the phase 3 study, 103SS, and the clinical pharmacology studies, 109 and 116, where the to-be-marketed presentation and updated PK assay were used and where steady-state PK concentration between hour to hour, day to day, and week to week are available.

We will first evaluate the hour-to-hour performance of ITCA 650, and then follow up with day-to-day and week-to-week performance in subsequent slides. These figures show the individual drug concentration time profile of exenatide for the ITCA 650 in Study 109 and 116. Four subjects from each study were selected as the most variable data observed.

The square and dashed line represent the drug concentration that is released by the 60-microgram per day device at steady state, whereas the circle and solid line represent the

drug concentration that is released by the 20-microgram per day device. The Y-axis is the exenatide concentration and the X-axis is the time of the collected PK sample in hours, starting on day 7 or 14 post-implantation.

These figures provide us two important observations. First, the drug release by ITCA 650 fluctuates unpredictably with time. Second, the magnitude of drug concentration change happens substantially high or low. As shown by the red arrow for subject 2, drug concentration can increase several thousand units over a 4-hour time span, and its concentration can be as high as 5,000 picograms per mL, or as shown by the blue arrow for subject 1, concentration can drop as low as 150 picograms per mL over an 8-hour time span. Overall, the data suggests a lack of consistent drug release by ITCA 650.

To further evaluate the drug release performance of ITCA 650 over a longer time interval, PK data from the phase 3 extension study, 103SS, was evaluated. Here, the figure shows the

individual concentration time profile of exenatide for the ITCA 650 product. Eight subjects from this study were selected as the most variable data observed. Each subpanel represents the PK sample taken at 3 consecutive days at week 41, 52, and 65 for each individual subject. The Y-axis is the exenatide plasma concentration.

If you look closely at the PK concentration for the three consecutive days for each subpanel, we can observe that some subjects have substantial fluctuation in drug concentration between days. These fluctuation are small. Similar to the observation from the previous slide, subject 19 on the top right, as highlighted by the red arrow, can have concentration change from 1800 to over 4,000 picograms per mL in a day and an immediate drop on the next day; or subject 12 with a 4-fold increase in concentration within 24 hours at week 65.

On the other hand, subject 1 on the top-left, highlighted by the blue arrows, can drop from 1600 picograms per mL to 500 picograms per mL.

Similarly, if you assess the PK data between different weeks within the same subject, variation in PK concentration change is also observed. These observations further support a lack of consistent drug release by ITCA 650.

Now that we have looked at the individual cases, we will now assess the methodology that was used by the applicant and CDER in the estimation of the within-subject variability. The applicant has estimated a within-subject variability of 29 percent in the background document to support that ITCA 650 has consistent drug delivery of exenatide; however, in CDER's assessment, this value represents the estimated month-to-month variability in the drug clearance.

Consequently, this month-to-month variability in clearance does not capture any sudden excursion or inconsistent drug release by the product within day and between day. In contrast, the within-subject variability estimate, based on individual concentration over 24 hours, represents a better approach to describe the

within-subject variability and to capture changes in the drug concentration within a day or between day.

In order to have a comparable approach in evaluating the within-subject variability in exenatide concentration between different studies and between products, we analyzed the PK data and calculated the within day and between day within-subject variability and exenatide concentration for both products. In this table, the within-subject variability represents the variability in concentration collected within the 24-hour time span in each subject, and the between day within-subject variability represents the variability in concentration collected at 3 consecutive days.

As you can see from the table, the estimated within-subject variability was 66 percent for ITCA 650 and about 20 percent for Bydureon. The between day within-subject variability ranged from 40 to 68 percent for ITCA 650 and 30 percent for Bydureon. In both cases, the ITCA 650 product

shows a higher within-subject variability as compared to Bydureon.

In summary, we have provided you CDER's insight on the methodologies that were used by the applicant and CDER on the in vivo performance of ITCA 650. We believe that the average trends from the exposure-response specifically for A1C are not a sensitive metric to capture the sudden excursion in drug concentration.

In addition, the mean drug concentration time profile may mask the fluctuation in concentration over time within the same subject. Thus, we need to assess the in vivo individual level PK data for ITCA 650, which shows inconsistent drug release with marked excursion in some subjects, which occur hour to hour, day to day, and week to week, and is consistent with the observation of the in vitro device performance for ITCA 650, showing variable exenatide release. Finally, the PK data suggests that the ITCA 650 product shows a higher within-subject variability as compared to Bydureon.

This concludes the clinical pharmacology review of ITCA 650. I will pass the presentation back to Dr. Archdeacon.

FDA Presentation - Patrick Archdeacon

DR. ARCHDEACON: Hello again. I'm Dr. Patrick Archdeacon, deputy director in the Division of Diabetes, Lipid Disorders, and Obesity. I'll give an overview of the design, demographics, and baseline characteristics of the ITCA 650 core clinical trials. The core trials include two glycemic control trials, CLP-103 and CLP-105, and an event-driven cardiovascular outcomes trial, CLP-107, known as FREEDOM.

CLP-103 was a double-blind, placebo-controlled trial that randomized subjects to one of three groups: the ITCA 650 20-microgram per day device followed by the 40-microgram per day device; the ITCA 650 20-microgram device followed by the 60-microgram per day device; or a placebo group that received sham devices. The 20-microgram per day, or sham devices, were removed and replaced with higher dose or sham devices at week 13. The

primary endpoint was change from baseline A1C to be measured at week 39. Enrollment criteria allowed for use of metformin, sulfonylureas, or TZDs as concomitant antihyperglycemic agents.

Importantly, subjects with a baseline eGFR less than 60 mL per minute per 1.7 meter-squared were excluded. Also, subjects taking metformin were excluded for a serum creatinine level greater than 1.5 mg per deciliter for males or greater than 1.4 for females. Importantly, the 4-week follow-up assessment was conducted 4 weeks after the subjects stopped treatment, not 4 weeks after week 39.

CLP-105 was a double-blind, active-controlled trial that randomized subjects to either ITCA 650 and a placebo pill or to sitagliptin and a sham ITCA 650 device. CLP-105 was an add-on study to metformin. Use of antihyperglycemic agents other than metformin was not permitted. The primary endpoint was change from baseline A1C to be measured at week 52.

Because CLP-105 ran for 52 weeks, an additional removal replacement procedure took place

at week 39. Subjects with a baseline eGFR less than 50 were excluded. In addition, males with serum creatinine greater than 1.5 and females with serum creatinine greater than 1.4 were excluded. Similar to CLP-103, the 4-week follow-up assessment was conducted 4 weeks after the subjects stopped treatment, not 4 weeks after week 52.

FREEDOM was a multicenter study to evaluate cardiovascular outcomes in subjects randomized to ITCA 650 or placebo. FREEDOM was an event-driven trial. The trial was to continue until 124 positively adjudicated MACE 4 events accrued. The inclusion criteria for FREEDOM were designed to enroll a population at higher risk of MACE events. Subjects were required to be at least 40 years of age with documented coronary artery disease or other ischemic vascular disease, or they were required to be at least 60 years old with cardiovascular risk factors in addition to type 2 diabetes. Subjects with baseline eGFR less than 50 were excluded. In addition, males with serum creatinine greater than 1.5 and females with serum

creatinine greater than 1.4 were excluded.

The composition of the core clinical trials were predominantly white, particularly in FREEDOM. The population of FREEDOM was older than the population of the glycemic control trial, though relatively few subjects 75 years or older were enrolled in any of the trials. Not surprisingly, the baseline characteristics of the FREEDOM population differed from those of the glycemic control studies. Subjects in FREEDOM had longer histories of diabetes. As per the exclusion criteria, no subjects in CLP-103 or CLP-105 used insulin, whereas 35 percent of the subjects in FREEDOM used insulin at baseline.

Whereas FREEDOM was enriched with subjects with established cardiovascular disease, very few subjects in either CLP-103 or CLP-105 had any history of ischemic vascular disease. Subjects in FREEDOM had greater use of statins, antiplatelets, and diuretics. ACE inhibitors and ARB use were common in all three studies.

As a consequence of the enrollment criteria,

few subjects in the ITCA 650 development program had moderate or severe chronic kidney disease. Less than 1 percent of CLP-103 and less than 5 percent of CLP-105 had a baseline eGFR less than 60. And although FREEDOM enriched its population with subjects with established cardiovascular disease, its exclusion criteria still resulted in the study population, with fewer than 10 percent of subjects with a baseline eGFR less than 60. Macroalbuminuria was present in only 6.7 percent of the subjects in FREEDOM.

In general, baseline characteristics in FREEDOM with respect to age, duration of diabetes, baseline A1C, and body mass index were similar to those of the other CVOTs. Some of the CVOTs enrolled subjects with established cardiovascular disease, whereas others, like FREEDOM, enrolled subjects with established cardiovascular disease or multiple risk factors for cardiovascular disease. ELIXA differed more markedly from the other cardiovascular trials in that it enrolled subjects who had experienced an acute coronary syndrome

event within the previous 6 months.

A notable difference between FREEDOM and the other GLP-1 receptor agonist CVOTs, is its limited enrollment of subjects with moderate-to-severe chronic kidney disease. Whereas only 10 percent of subjects in FREEDOM had a baseline eGFR less than 60, the other studies enrolled a higher proportion of such subjects, ranging from 22 percent to 31 percent.

Moreover, among the limited group of subjects in FREEDOM with baseline eGFR less than 60, most had a baseline eGFR relatively close to 60. The difference between FREEDOM and the other CVOTs, with respect to the enrollment of subjects with advanced renal impairment, is even more pronounced when one considers the representation of subjects across the range of eGFRs that meet the definition of moderate-to-severe renal impairment.

In CLP-103, approximately 20 percent of subjects prematurely discontinued treatment in each of the study arms, so the reasons for treatment discontinuation differed. In the ITCA 650

treatment arm, treatment discontinuations were driven by adverse events, and although more than 90 percent of subjects completed a 4-week follow-up visit after treatment discontinuation, most subjects who discontinued prematurely did not complete the other remaining study visits. As will be discussed in the clinical efficacy presentation, this resulted in high rates of missing endpoint data.

CLP-105 is the only completed phase 3 study in the development program that compared ITCA 650 to an approved antihyperglycemic agent. In this 52-week study, more subjects discontinued ITCA 650 than discontinued sitagliptin, 23.9 percent versus 18.7 percent. In addition, more subjects discontinued ITCA 650 than sitagliptin due to adverse events, 11.6 percent versus 3.7 percent. Although 92.5 percent of subjects completed a follow-up visit, the follow-up visit occurred 4 weeks after the subject discontinued treatment, not 4 weeks after the end of study. And as with CLP-103, most subjects who discontinued prematurely

did not complete other remaining study visits, resulting in high rates of missing endpoint data.

FREEDOM was an event-driven trial with a median follow-up time of 1.4 years. In FREEDOM, 17.8 percent of subjects randomized to ITCA 650 compared to 14.2 percent of subjects randomized to placebo discontinued treatment before the end of the study; 12.4 percent of subjects randomized to ITCA 650 discontinued prematurely due to an adverse event compared to 5 percent of subjects randomized to placebo.

I will now invite Dr. Wenda Tu from the Office of Biostatistics to present the efficacy review of Studies 103 and 105.

FDA Presentation - Wenda Tu

DR. TU: Thank you, Patrick.

Hello, everyone. My name is Wenda Tu. I'm the statistical reviewer of this application. I will be summarizing the efficacy of ITCA 650 from the CDER review of the two phase 3 pivotal trials, CLP-103 and CLP-105. Here's an outline from my presentation.

As Dr. Archdeacon has already walked through the details of the study design, just a quick recap here. CLP-103 was a superiority trial controlled on placebo, while CLP-105 was a noninferiority trial with the active comparator sitagliptin. Further, superiority to sitagliptin would be formally tested if noninferiority was successfully demonstrated in CLP-105.

The prespecified and multiplicity adjusted efficacy endpoints are listed here. The primary endpoint was changed from baseline A1C at 39 weeks for CLP-103 and at 52 weeks for CLP-105. The secondary endpoints include change from baseline in body weight, as well as binary endpoints derived based on prespecified A1C targets and the body weight reduction target.

For both studies, the applicant's analysis set consisted of randomized and treated subjects with valid baseline A1C value and at least one post-baseline A1C value. This approach does not follow the ITT principle by which all randomized subjects should be included in the analysis,

regardless of post-baseline status.

For the primary efficacy analysis, an ANCOVA model and an MMRM model was applied for studies CLP-103 and CLP-105, respectively. Missing data were imputed with LOCF for CLP-103 and by missing at random with the MMRM analysis for CLP-105. Although this was prespecified, both imputation methods may overestimate the treatment effect and are not recommended anymore. The LOCF ignores the uncertainties associated with missing data and MMRM assumes missing at random, an unlikely scenario in many clinical trials, as missingness may be related to unobserved clinical outcomes.

Another issue is that the applicant labeled the study visits by sequential visit numbers instead of prespecified visit windows. As a result, some visits were counted at time points far away from the intended visit days. For example, a visit at day 439, almost 8 months away from week 26, was counted as a week 26 visit.

Due to the limitations in the applicant's analysis, the CDER reviewer re-evaluated the

efficacy of ITCA 650 based on the methods described here. For both studies, CDER's analysis set included all randomized and treated subjects. For the analysis model, an ANCOVA was applied to both studies. To handle missing data, the reviewer used multiple imputation based on the return to baseline method, and to define visit windows, the reviewer used a window size of 25 days. The per protocol definition of window size was 7 days, which would result in a very high missing rate up to 31 percent.

The applicant's sequential labeling of the visit days, as previously explained, have around 20 percent missing data. Considering that the visits were generally scheduled 7 days apart, by using a window size of 3.5 weeks, we could assign each observation to a non-overlapping visit window that was closest to the time it was recorded. Our approach yielded up to 22 percent missing data.

Here are the primary efficacy results. For study CLP-103, the placebo-adjusted A1C change from baseline at week 39 was negative 1.0 percent for

the 40-microgram per day arm and negative 1.1 percent for the 60-microgram per day arm based on the applicant's analysis, and was negative 0.7 percent for both arms based on the CDER reviewer's analysis. All the results here are highly statistically significant. As a reminder, the 40-microgram device was not being proposed for marketing.

In study CLP-105, the treatment difference against sitagliptin was negative 0.7 percent based on the applicant's analysis and negative 0.4 percent based on the CDER reviewer's analysis. Both results established superiority of ITCA 650 compared to sitagliptin. Two things to note here for both efficacy studies: first, the estimated treatment effects or difference based on CDER's analysis were of less magnitude than the applicant's analysis; second, all the results here were based on the efficacy data sets with a missing rate as high as 23 percent. With this degree of missingness, it remains uncertain how reliable the magnitude of the estimated results can be despite

the updated missing data multiple imputation method used in CDER's analysis.

Moving on to the efficacy result on body weight, for the 60-microgram per day arm in particular, the placebo-adjusted body weight change from baseline was negative 2.0 kilograms based on the applicant's analysis and negative 2.2 kilograms based on the CDER reviewer's analysis. Both results were statistically significant.

And similarly, for Study CLP-105, both the applicant's and the reviewer's analysis results were statistically significant.

To summarize, the results from the CDER reviewer's analysis support the conclusion that ITCA 650 was efficacious when compared to either placebo or sitagliptin. Statistically significant treatment effects were found in both A1C change from baseline and body weight change from baseline when compared to placebo or sitagliptin, although the results from the reviewer's analysis were generally of smaller magnitude and have larger variability than those from the applicant's

analysis. Nevertheless, due to issues such as high missing data rate and mismatched visit windows, how to determine a reliable estimate for the underlying treatment effect is unclear.

That's the end of my presentation. Now, I'll pass it to Dr. Michelle Carey for the clinical safety presentation. Thank you.

FDA Presentation - Michelle Carey

DR. CAREY: Good afternoon. My name is Michelle Carey. I'm associate director for Therapeutic Review in DDLO, and I will be giving the clinical safety presentation and a summary of CDER's overall conclusions. Over the next 45 minutes, we'll review gastrointestinal adverse events in FREEDOM; the acute kidney injury imbalance observed in the ITCA 650 clinical program with a focus on events in FREEDOM; followed by review of AKI across all the GLP-1 receptor agonist CVOTs.

Next, we'll move to discussion of major adverse cardiovascular events, again with the focus on the FREEDOM results, and assess MACE data across

the other CVOTs in the class. We'll then review all-cause mortality and serious adverse events in FREEDOM and across the class. We'll close out with a summary of CDER's overall conclusions.

Moving into the first topic, gastrointestinal adverse events, the most common adverse reactions associated with GLP-1 receptor agonists are gastrointestinal; specifically nausea, vomiting, and diarrhea. The dosing schedule for approved GLP-1 receptor agonists, including the exenatide-containing products, generally includes a titration period of several weeks intended to gradually escalate exposures to mitigate GI tolerability issues. This is because rapid increases in drug exposures can cause GI adverse reactions.

Shown on this slide are events of nausea, vomiting, and diarrhea broken out by investigator-assessed severity in the FREEDOM trial. We focused this slide on FREEDOM due to limitations of pooling studies with disparate designs and also because FREEDOM contributed most

of the GI AEs in the clinical program given its larger size and longer duration. Adverse events of nausea, vomiting, and diarrhea were more commonly observed among subjects randomized to ITCA 650 compared with placebo, as reflected in the difference between treatment arms in terms of events per 100 patient-years, shown in the second column from the right, as well as the rate ratio shown in the far right-hand column.

We also evaluated the incidence of GI adverse events using two methods of time-to-event analysis. In these figures, ITCA 650 is represented by the red line and placebo by the black line. The left-hand panel displays time to first event of nausea and vomiting using the Kaplan-Meier estimator. The right-hand panel displays a recurrent time-to-event model that allows us to visualize cumulative events.

Looking at the left-hand panel, there is a bump in subjects experiencing first events of nausea/vomiting at treatment initiation with the 20-mcg per day device, and then again at 3 months

with uptitration to the 60-mcg per day device. Looking at the right-hand panel, there were increases in events of nausea/vomiting, including all events, not just the incident event, related to treatment initiation; uptitration at 3 months; and continuing forward in time, increases in events occurred related to subsequent device removal and insertion procedures, a staircase pattern at 6-month intervals.

There was also continued accumulation of events outside of periods subsequent to recent device changes as seen in the continued upward slope between each 6-month interval. These data suggest that the risk of nausea/vomiting is not restricted to periods of treatment initiation or titration.

Moving on to the issue of acute kidney injury, a few preliminary points to help frame the discussion of the safety issue are shown here. First, AKI was evaluated as an adverse event of special interest based only on standard spontaneous adverse event reporting; in other words, by

querying the available safety data sets retrospectively. Specific prospective AKI ascertainment methods were not employed, such as a dedicated case report form for each event. Because of this, limited additional information is available for AKI events coded as non-serious, and we only have narratives for events that were coded as SAES.

The applicant specified that they queried the adverse event database to evaluate for AKI using the Acute Renal Failure Standardized MedDRA Query Narrow Scope. A narrow scope SMQ is a grouping of preferred terms that are highly likely to represent the condition of interest. For example, the terms "acute kidney injury" and "acute pre-renal failure" are among the terms comprising the acute renal failure SMQ, and I've listed the 18 preferred terms included in this SMQ at the bottom of the slide.

Using this query, CDER identified 46 subjects, or 1.8 percent, with 52 AKI events in the ITCA 650 treatment arms versus 25 subjects, or

1 percent, with 27 events in comparator arms. Looking only at AKI events coded as serious, 14 subjects, or 0.6 percent, who received ITCA 650 versus 4 subjects, or 0.2 percent, who received placebo had such events. All except one of these events occurred in the FREEDOM trial. Eleven of 14 AKI SAEs in the ITCA 650 treatment arms were preceded by gastrointestinal symptoms with clinical narratives consistent with dehydration precipitating the event. Seven events in the ITCA 650 treatment arm occurred in subjects who had the 20-mcg per day initiation device in place.

Although case narratives are not available for non-serious adverse events, we did have narratives available for all subjects who died during the trial. CDER reviewed death narratives for subjects who had AKI events that were coded as non-serious and identified 2 subjects in FREEDOM who died following these events that were coded as non-serious. Because the outcome was death, these AKI events should have been coded as serious.

Because almost all AKI SAEs occurred in

FREEDOM and because of differences in enrolled population and study design compared with the glycemic control trials, CDER focused further analyses of AKI on FREEDOM. We already discussed the standardized MedDRA query narrow scope that the applicant utilized to assess AKI. In addition to the applicant's specified AKI analysis, CDER interrogated the FREEDOM safety database with several approaches to evaluate serious and overall AKI. We used standardized MedDRA queries, both the narrow scope query that includes terms "highly likely" to represent a condition -- in other words, a specific search strategy -- and the broad query that includes all terms in the narrow query, in addition to terms that are less specific and increase the sensitivity of the query to detect all possible cases. In recent years, FDA has also developed FDA MedDRA queries with narrow and broad scopes.

To evaluate AKI in FREEDOM, we conducted queries using SMQs and FMQs with narrow and broad preferred term groupings applied to both. We also

analyzed AKI events in FREEDOM using on-treatment censoring to capture only events that were treatment emergent and on-study censoring to capture events that occurred after treatment discontinuation while subjects were still being followed during the trial.

On this slide, shown is overall AKI events in each treatment arm, including both serious and non-serious events. As shown here, regardless of the query utilized or censoring scheme applied, the imbalance in AKI events unfavorable to ITCA 650 is apparent. The red box highlights the incidence rate difference between treatment arms and the point estimates of the hazard ratio, which are greater than 1.6 for every analysis with a lower bound of the 95 percent confidence interval that excludes 1, regardless of the search strategy or censoring scheme utilized.

This slide shows the same analyses for serious AKI events only in each treatment arm. The same pattern is apparent in that regardless of the query or censoring scheme applied, the imbalance in

AKI events unfavorable to ITCA 650 is seen, with the point estimates of the hazard ratios suggesting an approximately 3-to-3.5-fold increased risk of serious AKI events among subjects who received the product.

This slide shows key clinical features regarding the serious AKI imbalance. The applicant has pointed to baseline risk factors among subjects who received ITCA 650 as potential confounding factors in individual cases; however, baseline risk factors, including concomitant medications and presence of baseline renal impairment, were balanced between treatment arms due to randomization.

As noted previously, review of narratives identified that 11 subjects who received ITCA 650 experienced GI symptoms preceding development of the serious AKI event. In terms of timing of these events, AKI SAEs occurred at time points, ranging from the day of a device placement or replacement, out to 109 days after a device replacement in the ITCA 650 treatment arm. Two subjects in the

ITCA 650 treatment arm required dialysis. One of these subjects events was coded as serious. The other was a subject who died in the setting of an AKI event coded as non-serious. One subject in the placebo arm required dialysis.

What do these data actually mean to a clinician treating patients with type 2 diabetes?: For the more clinically relevant events of serious AKI, the FREEDOM data suggest an estimated number needed to harm of 322 patients treated with ITCA 650 per year to result in one additional serious AKI event. Given the millions of patients with type 2 diabetes in this country, if the product were taken widely, the risk of excess AKI is substantial. In addition, FREEDOM enrolled a low proportion of subjects with baseline chronic kidney disease, such that in a more susceptible population, the risk would be expected to be higher.

Shown here is a Kaplan-Meier plot for serious and non-serious AKI events in FREEDOM using the acute renal failure SMQ narrow scope with

on-treatment censoring. ITCA 650 is represented in red and placebo in black. As you can see, the two curves separate early on in the study and remain separated throughout, with events continuing to accrue over time, rather than being isolated to the time of treatment initiation or dose uptitration.

Finally, the applicant has contended that AKI is a class risk and that the imbalance seen in FREEDOM is not isolated among CVOTs in the class. We interrogated the safety databases for the CVOTs of the approved GLP-1 receptor agonist products with the same SMQs and FMQs as were applied to FREEDOM with on-study censoring.

Shown here are the results using the acute renal failure SMQ narrow scope, which was the applicant's specified AKI analysis. FREEDOM results are denoted by the red arrows to the left of the figure. The only CVOT that showed an imbalance in AKI is FREEDOM.

Dr. Archdeacon showed this slide of baseline characteristics of subjects enrolled in all of the GLP-1 receptor agonist CVOTs earlier. Again, the

proportion of subjects of baseline renal impairment enrolled in FREEDOM was lower than that enrolled in any other CVOT in the class, and no subjects in FREEDOM had an eGFR less than 45. So the AKI imbalance in FREEDOM was detectable, even in the population that may be less susceptible to AKI at baseline, compared with those enrolled in other CVOTs.

We wanted to discuss two other CVOTs in the class that the applicant has cited as demonstrating an AKI imbalance similar to that observed in FREEDOM. First, we'll discuss LEADER, the liraglutide CVOT. The applicant cited specific sources in their background document to support their statements that LEADER had an AKI imbalance, including Novo Nordisk's EMDAC briefing document and CDER's presentation to EMDAC in 2017. We thought it was important to show the original source data and explain why we don't agree these support a conclusion of an AKI imbalance in LEADER.

This is Nova Nordisk's table presenting AKI data cited by the applicant. Not surprisingly,

LEADER captured many more AKI SAEs than FREEDOM. LEADER was a trial about twice the size of FREEDOM and with about twice the median duration of follow-up. LEADER enrolled a population with about twice the proportion of subjects with moderate-to-severe renal impairment compared to the FREEDOM population.

In Novo Nordisk's analysis of acute renal failure presented in their EMDAC briefing document, they presented SAEs, events coded as severe, fatal, or leading to permanent discontinuation of trial product. Highlighted here is the row displaying acute renal failure SAEs. 141 subjects, or 3 percent, had 164 AKI SAEs in the liraglutide arm versus 136 subjects, or 2.9 percent, who had 153 AKI SAEs in the placebo arm.

In terms of overall acute renal failure events in each of the categories noted in this table, 156 subjects, or 3.3 percent, had 179 events in the liraglutide arm and 152 subjects, or 3.3 percent, had 171 events in the placebo arm. So again, even though many more acute renal failure

events were captured in LEADER compared with FREEDOM, there was no imbalance between treatment arms.

This is the slide in CDER's EMDAC presentation regarding LEADER that discusses death due to non-cardiovascular renal disease. This information was actually presented during the efficacy review because the composite endpoint proportion of patients with nephropathy at end of trial was an adjudicated efficacy endpoint in LEADER, with the four components shown here: new onset of persistent macroalbuminuria; persistent doubling of serum creatinine; need for CRRT; and death due to renal disease.

So the renal deaths the applicant cites actually refer to the component of this efficacy endpoint shown in the last row of this table. There were 11 deaths classified as non-CV renal deaths in the liraglutide arm and 5 deaths in this category in the placebo arm, with review of narratives indicating most were related to worsening of chronic renal failure. The CDER

presentation also noted there were no clear cases of liraglutide-induced GI losses leading to acute renal failure deaths.

Moving on to SUSTAIN-6, the applicant also presented some specific data available on clinicaltrials.gov from the SUSTAIN-6 trial with regard to AKI at the semaglutide 0.5-milligram dose. We wanted to show the full data set available at clinicaltrials.gov to make clear that there was no imbalance in AKI observed in that trial. The semaglutide 0.5-milligram dose is shown in the second column, next is the 1-milligram dose, followed by placebo 0.5 and 1-milligram doses.

We tallied up subjects and events with preferred terms in the acute renal failure SMQ narrow scope in the clinicaltrials.gov data set. First, as highlighted in the two red boxes, there were 26 subjects, or 3.1 percent, with 30 AKI SAEs in the semaglutide 0.5-milligram arm and 18 subjects, or 2.2 percent, with 18 events in the placebo 0.5-milligram arm. So this is where the numbers the applicant presented in their background

document were derived from; however, those numbers excluded the data from the semaglutide 1-milligram and placebo 1-milligram treatment arms.

As highlighted in the two blue boxes, there were 10 subjects, or 1.2 percent, with 12 events in the semaglutide 1-milligram arm and 24 subjects, or 2.9 percent, with 26 events in the placebo 1-milligram arm. As shown in the last row of this table highlighted in green, overall, there were 36 subjects out of 1648, or 2.2 percent, with 42 events in the pooled semaglutide arms versus 42 subjects out of 1649, or 2.5 percent, with 44 events in the pooled placebo arms. Note also that all subjects who were randomized to 1 milligram started at the lowest semaglutide dose and uptitrated to 0.5, then 1 milligram.

Also, just to clarify, there was no prespecified safety analysis plan to compare each separate semaglutide dose to placebo, although descriptive analyses of the separate doses were planned to be presented, and also additional analyses that included the pooled analyses were

also prespecified in no particular order. These data do not represent an imbalance in AKI SAEs in SUSTAIN-6.

CDER had previously evaluated the LEADER and SUSTAIN-6 data during the first formal dispute resolution request, and results of those analyses are shown here for those two CVOTs plus FREEDOM, evaluating SMQs narrow and broad scope and FMQs narrow and broad scope for serious and overall AKI events in all three trials.

For all analyses of AKI data in SUSTAIN-6 outlined in the red box, whether looking at overall events or serious only, the point estimates for the hazard ratio are less than 1, whereas for FREEDOM, the point estimate for all of these analyses is greater than 1, and for several analyses, the lower bound of the 95 percent confidence interval excludes 1.

Finally, the applicant pointed out that subjects with GI AKI SAEs in LEADER and SUSTAIN-6 had repeat AKI SAEs, whereas no subject in their program did. We disagree with that statement and

note that narratives for 3 subjects with AKI SAEs in the ITCA 650 program described repeat hospitalizations for AKI, including for one subject who died after requiring dialysis.

Class labeling for GLP-1 receptor agonists includes a warning and precaution for AKI based on postmarketing reports for Byetta and Victoza. Although the causal relationship between AKI and use of these other products has not been firmly established, the narrative case reports suggested AKI in the setting of adverse gastrointestinal reactions leading to dehydration and volume depletion.

Because GI adverse reactions are caused by the class, generally, FDA instituted class-wide labeling; however, these case reports cannot be used to determine the magnitude, incidence, or prevalence of AKI among patients treated with GLP-1 receptor agonist products because of the lack of a denominator with which to calculate these parameters and because of limitations of voluntary adverse event reports, such as incomplete or

duplicate reports, underreporting, reporting stimulated by publicity or litigation, and observations that could reflect concomitant treatment.

No approved GLP-1 receptor agonist products for treatment of type 2 diabetes had an AKI imbalance in their randomized-controlled premarket or postmarket clinical trials, suggesting that the AKI risk may be greater with ITCA 650 versus approved products.

To summarize CDER's conclusions on AKI, an imbalance in overall and serious AKI events in subjects who received ITCA 650 versus comparators was identified regardless of the search strategy or censoring scheme utilized. This imbalance was apparent despite lower susceptibility of the FREEDOM population versus other CVOTs, given the lower number of CKD subjects enrolled in FREEDOM. For the more clinically relevant serious AKI events, the data suggests an approximately 3-to-3.5-fold increased risk, or a number needed to harm of 322, in a controlled setting in a

population with low background frequency of CKD. Most serious AKI events were preceded by GI symptoms.

The device and PK exposure data demonstrated the potential for abrupt increases in exenatide exposures that could reasonably cause GI AEs, leading to dehydration and AKI. Thus, the AKI signal could plausibly be related to treatment with ITCA 650. This safety issue should be addressed via submission of additional premarket clinical data to demonstrate that ITCA 650 is not associated with excess AKI risk.

Now, we'll turn to discussion of major adverse cardiovascular events. At the time the ITCA 650 clinical program was designed, including FREEDOM, the provisions of the 2008 CV risk guidance for new anti-diabetic products were being followed. The guidance stated premarket safety data should show that the upper bound of the 95 percent confidence interval for important cardiovascular events is less than 1.8, i.e., excludes an 80 percent increase in risk. The

guidance also had language to underscore that ruling out the upper bound of the confidence interval of 1.8 is not sufficient in and of itself, stating sponsors should consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase. For example, it would not be reassuring to find a point estimate of 1.5, a nominally significant increase, even if the 95 percent upper bound was less than 1.8.

Finally, the guidance stated that if the upper bound of the confidence interval is between 1.3 and 1.8 and the overall benefit-risk assessment supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the confidence interval is less than 1.3.

Issuance of the 2008 guidance resulted in widespread conduct of CVOTs to evaluate new anti-hyperglycemic agents, including all of the GLP-1 receptor agonist CVOTs. The ITCA 650 clinical development program was designed, based on

CDER advice, to meet the provisions set forth in the 2008 guidance. All suspected CV events in the phase 3 trials were reviewed and adjudicated by an independent cardiovascular endpoint adjudication committee, and the applicant conducted a dedicated premarket, event-driven CVOT in a population enriched for risk of CV events, FREEDOM.

The applicant designated 4-point MACE, which was CV death, non-fatal MI, non-fatal stroke, and unstable angina as the primary composite CV variable and 3-point MACE, or CV death, non-fatal MI, and non-fatal stroke as a secondary composite CV variable in their CV safety analyses.

Analyses for pooled MACE data from all three studies and FREEDOM individually using Cox proportional hazard models were time to first occurrence of any event in the 4-point MACE composite, time to first occurrence of any event in the 3-point MACE composite, and the following censoring schemes were applied: analyses of events that occurred at any time during study participation, which is end of study or on-study

censoring; analysis of events that occurred up to 30 days after treatment discontinuation, which is end of treatment plus 30 days or on-treatment plus 30 days censoring; analysis of events that occurred prior to treatment discontinuation, which is end of treatment or on-treatment censoring. Other CV outcome variables assessed included first occurrence of any event in the composite of all-cause mortality, non fatal MI, or non fatal stroke, and the individual endpoints of CV deaths, non-fatal MI, non-fatal stroke, unstable angina, and all-cause mortality.

FREEDOM was designed to continue until 124 positively adjudicated events were collected across FREEDOM and the two glycemic control trials. For the planned pooled analyses, similar event ascertainment strategies were used -- for example, adjudication of events in all trials -- however, there are challenges in interpreting pooled analysis due to differences in the enrolled trial populations of type 2 diabetes. The glycemic control trials enrolled younger healthier subjects

at low CV risk, whereas FREEDOM enrolled older subjects at high CV risk. There were also differential follow-up times due to study designs. The glycemic control trials utilized a fixed endpoint, A1C at 6 months, whereas FREEDOM was an event-driven trial.

First, we present analyses of time to first events of 3- and 4-point MACE with on-study censoring. The first two rows of this table show results of the pooled analyses of the glycemic control trials and FREEDOM, while the second two rows show analyses of 3- and 4-point MACE with on-study censoring for FREEDOM individually. Note that there were 160 positively adjudicated 3-point MACE events in total, but the glycemic control trials only contributed 6 events to the pooled analyses, which is unsurprising, given the baseline low risk of CV events among subjects enrolled in these trials.

The point estimates of the hazard ratios and 95 percent confidence intervals are shown in the far right-hand column. For pooled 4-point MACE,

the prespecified primary efficacy variable, the point estimate was 1.12 with an upper bound of the 95 percent confidence interval of 1.5. For analyses of FREEDOM individually, the point estimates of the hazard ratio for 3-point and 4-point MACE are 1.24 and 1.21, respectively.

Next, we present the pooled analyses of time to first event of 3-point and 4-point MACE with on-treatment censoring. Again, the first two rows of this table show results of the pooled analyses and the second two rows show analyses of FREEDOM individually. Point estimates of the hazard ratios and confidence intervals are displayed in the far right-hand column. Using on-treatment censoring, the hazard ratio point estimates for 1.24 and 1.2 for pooled analyses of 3-point and 4-point MACE, respectively, these hazard ratios were 1.36 and 1.29 for 3-point and 4-point MACE looking at FREEDOM individually.

This is a Kaplan-Meier plot for time to first occurrence of 3-point MACE in FREEDOM using on-study censoring. In this figure, placebo is

shown in red and ITCA 650 in black. As you can see, the two curves separate early in the trial and remain separated throughout, as events continue to accrue throughout the trial. In contrast, the Kaplan-Meier curve for GLP-1 receptor agonist products that have demonstrated CV benefit, as reflected in their indications, the curves separate early in favor of the GLP-1 product and remain separated throughout.

We also evaluated key subgroups who are more susceptible to MACE, subjects greater than or equal to age 65 and subjects with baseline moderate renal impairment. Estimates of CV risk were higher in these key subgroups in the pooled analyses and for FREEDOM individually. In subjects greater than age 65 years, the lower bound of the 95 percent confidence interval nominally excluded 1 for all analyses. In practice, these subgroups may be more susceptible to a drug effect that increases CV risk.

This slide presents the individual components of 3-point MACE with three censoring

schemes and demonstrates that the overall imbalance in 3-point MACE was driven by the differences in events of CV deaths, shown in the first row, and non-fatal MI, shown in the second row, while non-fatal stroke, shown at the bottom, was neutral.

This slide presents in tabular form the point estimates and confidence intervals for the hazard ratios for 3-point MACE, 4-point MACE, and all-cause mortality across all the GLP-1 receptor agonist CVOTs. The FREEDOM results are outlined in red. We'll show this information graphically in a couple of slides as well. Except for ELIXA, the hazard ratio point estimates for all the other CVOTs was less than 1, including EXSCEL, which also studied an exenatide-containing product. We placed ELIXA to the far right in this table because it enrolled a different population of post-acute coronary syndrome subjects with type 2 diabetes and also studied a short-acting product.

We'd like to point out that when the 2008 guidance was published, the assumption under which all of these trials were designed was that the true

hazard ratio for CV events would be 1. Now with this robust data set of trials evaluating subjects with type 2 diabetes at risk of CV events, we would anticipate most GLP-1 receptor agonist products would have a point estimate of the hazard ratio between 0.8 and 0.9. Finally, we also note that the other trials displayed here that were relatively shorter duration, similar to the duration of FREEDOM, such as PIONEER-6 and HARMONY, yielded hazard ratio point estimates closer to what we would anticipate based on the class.

Very briefly, we wanted to clarify the ELIXA precedent the applicant referenced. The analysis the applicant had presented in their background document as a post-approval analysis was in fact the final analysis of the full ELIXA results that were considered for initial approval of lixisenatide in the U.S. The publicly available regulatory history is summarized on this slide. An NDA for lixisenatide was initially submitted in December 2012 with an interim ELIXA analysis for the primary composite 4-point MACE, yielding a

point estimate and upper bound of the 95 percent confidence interval for the hazard ratio of 1.14 and 1.47, respectively.

The applicant decided to withdraw the NDA in September 2013, stating that CDER's evaluation of lixisenatide should be based on the complete ELIXA results rather than interim data. An NDA was subsequently submitted and approved in 2016 with the final hazard ratio showing neutral CV effect. So again, in the U.S., lixisenatide was not approved with only the interim analysis available for CDER review. In addition, as mentioned, ELIXA was different from FREEDOM in that it was a trial in a post-ACS population and studied a short-acting product.

We also conducted a meta-analysis for 3-point MACE, including results of the published CVOTs of the marketed GLP-1 receptor agonist products, plus AMPLITUDE, studying efpeglenatide, and FREEDOM, and found that ITCA 650 appears different from other products in the class with respect to CV outcomes. Our meta-analysis

calculated results using both a common effect model and a random effects model. The two statistical approaches yielded nearly identical results.

As shown in this figure, the individual CVOT results for all of the other long-acting GLP-1 receptor agonist products are consistent with the overall estimate based on the meta-analysis. The point estimate for the hazard ratio for 3-point MACE of each of these 7 CVOTs, denoted by the red bracket, is close to or below the point estimates of the meta-analysis.

Again, we have ELIXA at the top evaluating a short-acting product conducted in a post-ACS population, which was the only other trial that did not have a point estimate of the hazard ratio below 1, and FREEDOM is at the bottom, noted by the red arrow, which is dissimilar from the others and an outlier based on a comparison with other CVOTs.

In addition, the lower bound of the 95 percent confidence interval for 3-point MACE for FREEDOM was 0.9, which is higher than the point estimate for the hazard ratio for the other GLP-1

receptor agonist agents, based on the meta-analysis, with a point estimate of 0.87 or 0.86. This raises significant concerns that ITCA 650 is distinct and results in substantial uncertainty about the CV safety of the product.

Because we observed there were more deaths in the ITCA 650 arm versus placebo in FREEDOM, we also conducted a meta-analysis for all-cause mortality across the class CVOTs shown here. Again, FREEDOM is denoted by the red arrow. Clearly, there were fewer events in FREEDOM compared to the other CVOTs as reflected in the wide confidence interval that overlaps with the confidence intervals for the hazard ratios for the other trials; however, the FREEDOM results again appear dissimilar from the others.

To summarize CDER's conclusions on MACE, primary and secondary endpoint analyses and all other prespecified analyses of CV risk, regardless of pooling or censoring scheme utilized, provide consistent findings. Results of FREEDOM, a dedicated CVOT enrolling patients with type 2

diabetes at high CV risk, do not adequately exclude the possibility that ITCA 650 is associated with excess risk of CV harm. Although most of the analyses exclude an 80 percent increase in the risk of CV harm, not all do, and the point estimates of the observed hazard ratios are not reassuring.

FREEDOM is an outlier among the many other long-acting GLP-1 receptor agonist CVOTs. The lower bound of the 95 percent confidence interval for MACE was 0.9, which was higher than the point estimate of the hazard ratio observed in most individual GLP-1 receptor agonist CVOTs and in our meta-analysis. This raises concern that ITCA 650 CV safety profile is distinct from that of other GLP-1 receptor agonists and also fails to provide reassurance that ITCA 650 is not associated with an increase in CV risk.

Overall, in the context of the in vitro and PK data, and other unfavorable imbalances in clinical outcomes -- AKI, serious adverse events, all-cause mortality -- as well as the larger context of the GLP-1 receptor agonist class in

which several products have demonstrated CV benefit, the MACE data from FREEDOM constitute a CV signal that requires additional premarket investigation to ensure patients treated with the product are not exposed to excess CV risk.

We also evaluated overall serious adverse events in FREEDOM. In FREEDOM, subjects randomized to ITCA 650 experienced a numerically higher incidence of SAEs than subjects randomized to the placebo control. 17.8 percent of subjects randomized to ITCA 650 experienced at least one SAE compared to 15.6 percent of subjects randomized to placebo. Given the observed imbalance, we conducted a hazard ratio analysis for the outcome of time to first SAE. As outlined in red, the point estimates of the hazard ratio nominally exclude 1, whether an on-treatment or on-study censoring scheme is applied. These data suggests an estimated number needed to harm of 45 patients treated with ITCA 650 per year to result in one additional serious adverse event.

We also evaluated serious adverse events

across all the CVOTs in the class with results displayed here and FREEDOM shown at the top. Again, FREEDOM's results appeared dissimilar from the other trials in the class, which yielded point estimates of the hazard ratio at or below 1 for all the other products.

Putting this all together, we've shared a lot of information today, but in the last two slides, I'll summarize CDER's review conclusions. We have a drug-device combination product for which device data demonstrate inconsistent exenatide release, even under ideal in vitro conditions, and the available PK data support the device review conclusions that exenatide release demonstrates high within-subject variability with the potential for rapid excursions.

From the efficacy perspective, this product has demonstrated efficacy based on its glycemic lowering effect, but from the safety perspective, we have clinical safety data that are concerning, especially considering the therapeutic context of available GLP-1 receptor agonist therapies. The

AKI signal is concerning and plausibly related to treatment with ITCA 650, based on the available device and clinical pharmacology data, as well as review of the narratives, suggesting GI AEs precipitated most events. The product has MACE results that are dissimilar to findings from other large CVOTs in the class, and overall SAEs and all-cause mortality trend unfavorably, also distinct from the class.

In terms of an overall benefit-risk assessment for this product, on the benefit side, we have glycemic efficacy and the potential for advantages inherent to the product presentation for some patients; however, long-term adherence sufficient to improved outcomes compared to other approved products in the class has not been demonstrated. In terms of risks, we have an AKI safety signal in the setting of inconsistent device release, PK variability, and GI AEs. We have a non-reassuring CV risk assessment and unfavorable trends in serious adverse events and all-cause mortality.

Overall, these significant uncertainties regarding the safety of ITCA 650 should be addressed through submission of additional premarket data to ensure patients treated with the product are not exposed to excess risk of harm. I'll close the CDER presentations here, and we look forward to taking questions from the committee. Thank you.

Clarifying Questions

DR. LOW WANG: Thank you for your presentations.

We will now proceed to clarifying questions for the FDA presenters. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. And finally, it'd be helpful to

acknowledge the end of your question with a thank you and the end of your follow-up question with a, "That is all for my questions," so we can move on to the next panel member.

I would like to ask a Dr. Meininger to please ask your question. Please state your name first.

DR. MEININGER: Hi. Can you hear me?

DR. LOW WANG: Yes.

DR. MEININGER: Okay. Great. Gary Meininger, industry representative. First of all, I want to compliment both the sponsor and the FDA for very clear presentations. Obviously, this is an unusual ADCOM in the sense that it's a state of trying to get to the bottom of facts and, obviously, the sponsor presented first, and then the FDA had some very nice rebuttals.

It would be helpful to hear potentially from the sponsor, particularly on some of these issues, but particularly what seems to be, at least from what I've seen from information, the AKI question and the signal, particularly as it relates to SAEs,

because it seems like they're essentially different facts, and it would be helpful to understand that. So maybe it's more of a question for the sponsor than the FDA to be able to rebut some of the presentation.

MR. GRAVES: Thank you. I'd like to address this starting off by the relative risk the FDA highlighted in their presentation, the 3-to-3-and-a-half-fold increased risk. I'd like to look at slide AK-3, please, to address the question.

So this slide shows you the same slides that Dr. Drucker and I presented. Our studies on the left there, our CVOT Study 107, you've got SUSTAIN-6, and then you've got two trials with semaglutide 2.4 milligram that we also presented. If you look at the relative risk ratio, again, I still want to emphasize the caution needed for cross-trial comparisons on all these numeric imbalances because they're small numbers for each of these studies, but if you just show the facts, which is what you asked for, you can see that the

relative risk is not out of line with what's seen. The highest actual risk is seen with a 5-fold increased risk in the study that was just published four weeks ago in the New England Journal of Medicine with STEP heart failure.

So that gives you a sense -- the other reason why the agency apparently is claiming a 3-to-3-and-a-half-fold increased risk in serious AKI for us -- which we had not heard before this hearing, that was not in any of our CRLs -- is because they've -- I don't know a better word to use; they increased the numbers beyond what we've discussed with them previously in our formal dispute resolution.

There were two cases that Dr. Drucker presented in detail -- I can go through those if the panel would like -- where the FDA just presented again that a person who actually died from a coronary event had a serious AKI and GI side effects that didn't exist. That was not a death or a serious AKI event on our drug. It was someone who didn't have a serious AKI and died from a

coronary event, and there were no GI side effects involved. That event being used to increase the risk to a 3-to-3-and-a-half-fold risk is just not accurate.

The other case, which Dr. Drucker also presented --

DR. LOW WANG: Excuse me. I'd like to interrupt. I think this is a time for the FDA to receive questions from our panel members, so thank you so much for that response.

I would like to move on to the next --

MALE VOICE/INTARCIA: Could I respond to some of those comments or --

DR. LOW WANG: -- excuse me. I'd like to call on the next --

MALE VOICE/INTARCIA: I'm sorry. I'll let it go. Thank you.

DR. LOW WANG: Excuse me.

I'd like to call on the next panel member, Dr. Cooke, please.

DR. COOKE: Yes. For Dr. Chow, I thought the within-day variability data that you showed was

useful to see. I was interested to know, do you have similar PK data for exenatide levels with Byetta on the BID regimen to get an idea of the swings of exenatide that might be seen with that compared to this preparation?

DR. CHOW: Hi. This is Edwin Chow, clinical pharmacology team leader. Thank you for your question. Your question is asking the within-subject variability of Byetta BID.

From our assessment, you cannot really compare the two products because the ITCA 650 is a controlled release product, where the drug concentration is governed mostly by the drug release of the products, whereas Byetta is mostly for the sub-Q injection; once it gets absorbed, the drug concentration is determined by the distribution and administering of the drugs. So by comparing these two products, it's not feasible to compare the within-subject variability between days and within days.

DR. COOKE: I understand that, but at least for me, it would be helpful to see what kind of

peak exenatide level, after the Byetta, is compared to those higher levels seen in the variability with this product, just from a toxicity standpoint. Is there any data to compare that type of information?

DR. CHOW: Yes. I don't have a slide on this, but based on the PK property of exenatide, the half-life is about 2 to 3 hours. So for the Byetta biweekly injections, the concentration after a pre-dose is normally at a very low level and the the Cmax level is actually similar to the Bydureon level. Again, we cannot really compare because these are cross-trial comparisons using different PK assays, so we won't look at the absolute concentration value, but we do look at the variability of these products.

DR. COOKE: Okay. Thank you.

DR. LOW WANG: Thank you.

I'd like to remind the panel members to direct your questions to the FDA presenters, and please state your name for the record. So next, I'd like to call on Dr. Wang.

DR. WANG: Thanks very much. I just wanted

to ask two related questions on the cardiovascular risk, and this is to the last FDA presenter. One of the sponsor concerns in the FDA analysis was a comparison of the preapproval CVOT data to the post-approval CVOT trials, which are generally larger and longer, and they raised the example of the lixisenatide in which the early data suggested excess harm, but the later data, that was attenuated. And a good case was made that there were potential reasons that the lixisenatide may not be the best example, including the post-ACS population.

What I heard, and I just wanted to confirm, is that there really are no other examples in which there was preapproval CVOT data with a point estimate greater than 1, even if the upper limit was less than 1.8; that in all of the other drugs that have been approved by the FDA, that in general, this cardiovascular safety signal wasn't present, even in the preapproval state.

And secondly, related to that, a broader question, really, that was also raised by the last

presenter, which is now that we have a large body of data related to multiple classes of diabetes medications showing likely cardiovascular benefit, is a placebo control for the CVOT studies the best control going forward for CVOT studies for these classes of medications?

DR. CAREY: Thank you for those questions, Dr. Wang. Just to clarify, to your first question, what was characterized by the applicant in the background document as a preapproval MACE analysis was actually an interim analysis of ELIXA that was submitted with the initial NDA submission. The applicant of that product then chose to withdraw the NDA and resubmitted in 2016, three years later, when they had the full ELIXA results available. So the interim analysis was never considered for the final review for the approval; it was the full ELIXA results that were considered.

And the second part of your question about what type of trial could be done, we haven't had protocol discussions about a CVOT with this applicant. We're happy to, but a proposal hasn't

been made previously prior to these proceedings. We would certainly discuss those issues and consider them carefully. I think you raise an important question about the ethics of feasibility, is there equipoise for a placebo control?

DR. WANG: Thank you.

Next, I'd like to call on Dr. Nachman, please.

DR. NACHMAN: Yes. Patrick Nachman, nephrology. Thank you, Dr. Wang. I have two questions, if I may, that are somewhat related. My first question is to Dr. Wolloscheck, and it's a little bit the converse of the question that Dr. Cooke asked in the previous session.

The IVR was, as was mentioned, highly controlled in an idealized setting. Pardon my ignorance; I don't know how these osmotic pumps work, but the interstitial fluid is not constant and it's not idealized. Do you have any idea or can you educate me on what would happen if the patient became acutely hyperglycemic; or if in the setting of GI side effect they were to become

hyponatremic; or what would happen in a case where the patient is edematous, as frequently diabetics can be, especially if they have diabetic kidney disease? So what happens? How does the pump work in those situations?

DR. WOLLOSCHECK: Yes. Thank you very much, Dr. Nachman. This is David Wolloscheck from CDRH. Great question. I think osmotic pressure is a driving force for this device and the device relies on consistent influx of interstitial fluid to provide a consistent drug release. On your specific question, I don't think we have any specific data on that, so I would have to guess. But the osmotic pressure does control drug release, so I could only assume that if we have differences in osmotic pressure, such as due to dehydration, that could impact drug delivery further.

DR. NACHMAN: So if I may direct my next question to Dr. Carey, you raised and provided us with evidence that ITCA 650 behaves differently than the other GLP-1 receptor agonists with respect to CVOT or it seems to be dissimilar results. I'm

linking the data that suggests that there is somewhat of greater excursion in drug delivery with this pump than with, let's say, Bydureon or other injectable GLP-1 receptor agonists.

Do you have evidence or data, or maybe from way back when with exenatide studies, or maybe even preclinical studies, that somewhat links, let's say, toxic levels of exenatide or very high levels of exenatide with cardiovascular events? I mean, the class seems to be associated with decreased cardiovascular events, so why is it that this drug, which is the same drug as before, would behave differently? The one link in my mind would be that maybe if the pump is releasing peaks of drug that would be the precipitant to vasoconstrictive effect, thrombogenic effect, arrhythmogenic effect. Do you have any data in that regard?

DR. CAREY: Thank you for that question. It's a very good question. So we have thought about this. We know that, as you've said and as we've shown, many drugs have demonstrated CV benefit, and the mechanism of that is not

completely understood. We do know that GLP-1 receptors are expressed on vascular endothelium, for example, from nonclinical studies, but we don't know the full extent of where the CV benefit's coming from. We see that benefit starting to accrue even before glycemic lowering effects have been demonstrated in the trials where CV benefit was shown, so even that's not fully understood. We have some theories, but we don't have a clear mechanism of how inconsistent exenatide exposures would directly link to MACE, and we think that's an important question.

We'd also like to point out that what we're saying about the results of this product's CVOT is that it generates a lot of uncertainty about the CV safety. We haven't said that the CVOT definitively demonstrates CV harm and nor does it exclude a very small chance of CV benefit. If you look at the confidence intervals, they're rather wide. But we're saying is there's a lot of uncertainty here and the results are dissimilar from all the other trials in the class. That's where our concern is

coming from, and we think that this deserves additional premarket evaluation.

DR. NACHMAN: Thank you. No more questions.

DR. LOW WANG: Thank you.

Next, I'd like to call on Dr. Brittain.

DR. BRITTAIN: Yes. Hi. This is Erica Brittain, and my question, again, is for Dr. Carey. It's on slide 96. Anyway, first of all, great talk. The sponsor made a big point about how the follow-up pattern, the length of follow-up, was different for their study than these other studies, and it's certainly true if the treatment effect is changing over time; if you're comparing hazard ratios across different studies, it could be misleading.

The Kaplan-Meier curves you showed are very helpful to address that, but I guess what I'm trying to understand, is there any study on this page that has the same length of follow-up that would at least be pretty comparable to the FREEDOM study or are these all longer studies?

DR. CAREY: That's a good question. Yes,

there are other studies on this table and similar median duration to follow-up. For example, HARMONY, PIONEER-6, which was, I think, 1.4 years median duration, and ELIXA, which was about 2 years. HARMONY was also, I think, 1.8 years. So these were all a similar duration of follow-up as FREEDOM, and we've pointed that out because we still see these dissimilar results. So we don't think that hypothesis that had the FREEDOM trial been longer, that would have ameliorated this effect that we saw or changed the results is necessarily true, given that we do have these other examples of trials in the class of similar duration.

DR. BRITTAIN: Thank you.

DR. LOW WANG: Thank you.

Next, I'd like to invite Dr. Kalyani to ask your question.

DR. KALYANI: Thanks. Rita Kalyani. I actually had a question about the same slide, slide 96, for Dr. Carey.

DR. LOW WANG: You're welcomed to go ahead

and ask the question.

DR. KALYANI: Okay. Thank you for the great presentation. I just wondered on this slide, if you could point out -- I think I know offhand, but just to be correct -- which ones of these trials are premarketing versus postmarketing, because that also might impact interpretation of the conference intervals. Then, what do you think of the fewer relative events in FREEDOM versus these other trials and how that impacts the breadth of the confidence interval, and if that uncertainty that we're talking about might be related to perhaps relatively fewer events or if that point estimate is really what's driving your concern about uncertainty?

DR. CAREY: Thank you. The trials on this table that were postmarketing were EXSCEL, LEADER, and REWIND. The others were all available premarketing. I think you raise a really good point, and we tried to draw that out by pointing out the wide confidence interval surrounding the point estimate of the hazard ratio for FREEDOM. It

is a wide confidence interval.

We do have fewer events than were collected in some of the other trials, and that's why we think there is so much uncertainty here. You have a wide confidence interval that does not establish CV harm, does not also definitively exclude some small chance of CV benefit, but we have enough events and enough uncertainty here that we think that this should be evaluated premarket and that it's not appropriate to let this be evaluated further postmarket.

So I think you raised some really good points about the the weaknesses of the data that we've also struggled with, but this is what we're left with, and we think it's enough information to generate real serious concerns and uncertainty about the CV safety of the product.

DR. KALYANI: And I just had one other question related to the AKI ascertainment. You mentioned that in FREEDOM, it was based on spontaneous reporting. In other GLP-1 premarketing trials, is that the usual method or did they have

a priori adjudication?

DR. CAREY: That's a good question also. Different trials did different things, like, for example, LEADER looked at ARF SAEs, as well as non-SAE medically significant adverse events in the the renal function category. So they did do things differently depending on the trial but, again, obviously prespecifying is always ideal, and we do think that's part of the issue of why we collected so many fewer events in the ITCA 650 clinical program. I'd have to check and see the protocol for each of these and exactly how they defined it, but some did prespecify, and others did the retrospective analysis using SMQs, as the FREEDOM trial did.

DR. KALYANI: Thank you so much.

DR. ARCHDEACON: I think just for completeness, I wanted to clarify, HARMONY I think was also a post-market study --

DR. CAREY: Okay. Thanks.

DR. ARCHDEACON: -- but, yes, there are four that were premarket, AMPLITUDE, SUSTAIN, PIONEER,

ELIXA; and efpeglenatide has not actually been approved yes, but premarket.

DR. CAREY: Thanks.

DR. LOW WANG: Thank you so much.

We have just a few minutes before we break for lunch, so we have time for two more panel members to ask their questions. So next, I'd like to ask Dr. Everett to ask his question.

DR. EVERETT: Thank you. Brendan Everett. My question is specific to slide 22. I think it might have been Dr. Wolloscheck who spoke about it. If you can get the slide up, I think it's a relatively -- thank you for this slide. I wondered, looking at this, about the sponsor's contention that one of the challenges of measuring the concentrations of the drug on a day-to-day basis were real and that you could potentially miss it one day and have the concentration come out low, a viscous drop of drug, and then the next day you would end up with much higher concentrations just because, by chance and method of ascertainment, you missed it the prior day.

If I look at this figure, I can see how that actually might be the case. If you look at number 6 in the top-left, I think towards the right-hand side of that, first -- maybe it's around day 30 or so -- you can see there's a negative excursion and then a positive excursion, and I imagine if you average the two, they would be sort of right where they should be, on the line.

So my question for the FDA is how much stock do you put in that potential argument? Just looking at these data, it seems to have some validity to me, but I wanted to hear what your thoughts were about the question of the technical challenges of measuring the concentrations as a potential explanation for these excursions that you see on this slide.

DR. WOLLOSCHECK: Yes. Thank you, Dr. Everett. This is Dr. David Wolloscheck. That's a great question. Per the information that was provided by the applicant, the test method was validated for daily in vitro release testing, and based on that statement, we would not anticipate

there to be unreasonably variability due to the test methodology, essentially. Test methods should be validated prior to performing device design verification.

If that was a specific concern, I think there are other test methods that could have been developed that would be more sensitive. For example, this was quantified with HPLC. I think if that was a specific concern, one could have used things like mass spec, for example, to be more accurate in the quantification, if that is a concern; and if not, then the specific test methodology should be validated to provide accurate results.

DR. EVERETT: Thank you. That's it for me.

DR. LOW WANG: Thank you.

Next, I'd like to ask Dr. Konstam to ask your question. Please state your name for the record.

DR. KONSTAM: Thank you. Marv Konstam. First, I really want to congratulate the FDA speakers. They've obviously been looking as a team

at this drug-device combination for a long time, and they've acquired enormous expertise to try to get to the right answer.

I just want to speak to Dr. Carey for a second. The slide that you just took down -- I don't remember the number, but that shows -- not that one, but the one that shows all of the different studies and all of the point estimates below, well below 1, and then the standout; that one.

There are people who would say, well, if I just look at anyone -- like let's take the 1.90 with dulaglutide, the lower limit point estimate for FREEDOM is 0.79, and let's do all-cause mortality, is the one I'm looking at, which would say you haven't proven that it does harm. I compliment you for pointing out that you're not trying to ask is there proof of harm; you're trying to ask is there comfort of unlikelihood of harm.

I suggest one analysis you could do, if you haven't done it -- not that I think you necessarily need it but just think it would help further -- is

to do a Bayesian predictive model looking at the FREEDOM trial and ask, given the total data set in that trial, what's the probability that if it extended on to one of these larger trials, it would yield a point estimate that's discernibly less than 1?

DR. CAREY: That's a great point. Thank you very much. The only other thing I would add, as we've mentioned a few times, is that we do note that there were fewer events collected in FREEDOM compared to some of the other trials, and we do know that this is reflected in the wide confidence interval. And when you have the situation with imprecision surrounding the hazard ratio point estimate, the only way to resolve that is through additional clinical data, and that's what we're really saying here.

DR. KONSTAM: Sure. Agree.

DR. LOW WANG: Thank you.

Next, I'd like to ask Dr. David to ask his question.

(No response.)

DR. LOW WANG: I don't know if I said his name correctly, but maybe before -- I don't know if he's able to unmute his microphone -- if I could call on Dr. Wilson, then, next.

DR. WILSON: He was just jumping in. Peter Wilson here, Emory. My question is to the FDA, to Dr. Carey. Across all these trials, has there been a guidance from FDA for persons who have nausea and vomiting? For those of us who prescribe these drugs, this is a big issue. You have diabetics with nausea and vomiting, and now even with potential acute kidney injury, what about the persons who don't produce very much urine? Do they generally have hotline numbers to call, things like that? Was that ever considered for the FREEDOM trial as it was being laid out?

Where I'm going with this is, could there have been averted AKI incidents with a sense that, well, this person's just not making enough urine; you need to call this number, and we'll get you in to see your provider or we have a special team. And that may be part of -- I'm thinking, forward,

as you go forward with this -- something needs to change, especially for those that appear to be more renally cleared. That's the end of my question.

DR. CAREY: I think you're getting to a really important point, which is what risk mitigation strategies could we consider for the product. Could we bring up FDA slide 32, backup slide 32, please?

While that's being brought up, I'll just talk through what some of the risk mitigation strategies were that we considered in the review. We considered labeling strategies, potentially a REMS. In their NDA resubmission, the applicant had proposed, and as they mentioned today, to address the AKI risk through labeling, such as by limiting treatment with the product to patients with baseline eGFR greater than 45, recommending increased monitoring for GI symptoms during some initial time periods such as 30 or 60 days after implantation, or providing additional labeling language to inform prescribers of symptoms or laboratory findings that would trigger early device

removal.

We considered those, but we concluded that the risk of AKI couldn't be adequately mitigated via labeling or REMS. We noted that AKI SAEs occurred at times ranging from day 0 out to day 109 after device placement or replacement, so there was no clear time point after a placement or replacement that the risk of AKI substantially decreases and that we could describe in the product label or REMS educational materials.

Then we also noted that in the narratives of subjects who were admitted to the hospital with serious AKI events, even in the clinical trial setting, identification of the event and the potential that the event could be linked to treatment with the product didn't always occur, so there were significant delays in device removal in several subjects.

There were two who didn't undergo device removal until 4 and 2 days into their hospitalizations, respectively, and there was another subject who was initially admitted for AKI,

discharged with the device in place, and sent to a nephrologist 3 months later, and she still had an elevated creatinine. And it was at that time that the nephrologist recommended device removal and her creatinine returned to baseline.

So we thought through many of these strategies, but based on the data that we had reviewed from the trial, we determined that they wouldn't be adequate to ensure the benefits would outweigh the risks in the postmarket setting.

DR. WILSON: Yes. Thank you. That's very helpful.

One follow-up a little bit is, was the outpatient creatinine level updated during the course of these studies? We measure creatinine clinically every year. The FREEDOM trial is only 1.x years, but perhaps at 6 months is another consideration because the person's creatinine may mildly change, and that will affect decisions going forward for treatment as well.

DR. CAREY: Right. So creatinine was generally rechecked at the time of a device removal

and reimplantation. One example would be one of the subjects who died in the setting of an AKI event. The subject came in for a usual device replacement. The labs that were drawn that day noted a bump in the creatinine from 1.3 to 1.6 milligram per deciliter. The device had already been replaced. At that point, the subject had gone home, and the subject was called, instructed to stop metformin, and then was found dead 8 days later. So we found in the clinical trial setting, those types of strategies were not adequate to mitigate some of these events.

DR. WILSON: Yes. One last comment on that is the metformin dosage change has evolved since this scenario started. Endocrinologists are very in tune to this, but not all the clinical providers are aware the doses are ratcheted down.

DR. CAREY: Thank you.

DR. WILSON: Thanks.

DR. LOW WANG: Great. Thank you.

Before we break for lunch, I wanted to mention that we may have time after the open public

hearing for Dr. David's question.

We will now break for lunch and reconvene at 2:00 p.m. Eastern Time. Panel members, remember that there's no chatting or discussion of the meeting topics with other panel members during the lunch break, and additionally, you should plan to reconvene at around 1:50 p.m. Eastern Time to ensure that you're connected before we reconvene at 2:00 p.m. Thank you.

(Whereupon, at 1:30 p.m., a lunch recess was taken, and meeting resumed at 2:00 p.m.)

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

(1:30 p.m.)

Open Public Hearing

DR. LOW WANG: Good afternoon. We will now be starting the afternoon session and begin with the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

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

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

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

Speaker number 1, please unmute and turn on

your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

DR. DIRKES: Thank you. My name is William Dirkes, Jr., and I appreciate the time regarding approval of the ITCA 650, which I believe is an important part of the diabetes treatment armamentarium, based primarily on its effect on medication adherence. I have no financial relationship with Intarcia or the i2o Therapeutics companies.

I'm here today both as an anesthesiologist and a clinical investigator who was involved in several of the Intarcia ITCA 650 studies. As an anesthesiologist, I had insights to the ravages of medication nonadherence. This comes from seeing the many diabetic patients who came to the operating room for end-stage renal disease procedures, including kidney transplants, vascular access declots, as well as limb amputations, and a multitude of eye procedures. One frequent common

denominator to these patients was nonadherence.

As a clinical investigator for the ITCA 650 studies, one of the clear differences compared to other research studies was there's 100 percent adherence for the treatment group. In all diabetes trials, patients were likely nonadherent with their diabetes care before the study, as they needed to have a high A1C to become eligible to participate in the study. From the experience, I can tell you that enrolling in a clinical trial is advantageous, as even the comparator group often has improvements in their A1C because of improved adherence, but the key is, I do not believe that enrollment in a clinical trial yields a 100 percent adherence rate in all patients.

As an investigator, the question I have, is how do the numbers and statistics change if we consider that in the ITCA 650 placebo groups and those other GLP-1 trial treatment and placebo groups, the adherence rate was likely not 100 percent? My experiences with nonadherence rates for patients and studies may go from 50 to

70, or 80 percent, and patient-reported adherence is 80 percent or better, and that's generally considered a cutoff adherence rate, but adherence certainly is not 100 percent, which is what we know was present for the treatment arm of the ITCA 650 studies.

So when you make a comparison to other GLP studies, the adherence is assumed the same between the treatment group and placebo group; however, it's not likely 100 percent in either group. All the analyses presented today seem to assume a 100 percent adherence rate in all groups. In the ITCA 650 study's placebo groups and comparator GLP studies, the true treatment denominator is likely lower, and a true rate of complication is higher if adherence had been 100 percent.

Medication adherence can be improved with education, but due to human nature, it will never be 100 percent, except with this device. That 100 percent adherence is important in the research trial, and certainly in the real-world clinical realm. Thank you again for your time and

consideration.

DR. LOW WANG: Thank you.

Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

DR. BUSCH: My name is Robert Busch. I'm an endocrinologist in Albany, New York at Albany Medical Center, and I'm the director of clinical research here. Obviously, you're going to hear from all of the speakers about adherence and persistence because we know having a medication on paper versus having the patient put it in their mouth or take the injectable are very different, and we know that with GLPs particularly, the adherence rate is not that terrific. Even though the patient may start out doing well, it's felt maybe 20-30 percent of patients don't adhere to their medication when you probe them why their numbers aren't good or why they gained weight since the last visit.

Being in all the GLP studies, we have 312 in the EXSCEL trial and we know the adherence in that trial was the worst of all because of the pen device that was 17 complicated steps followed by a harpoon. If the patients took the drug, probably the EXSCEL trial would have been positive for that reason, if they took it, and because of the SGLT2 drop-in in the placebo group.

We had an FDA review for the SUSTAIN-6 trial with Ozempic for its cardiovascular trial, so like many of the people who will talk today, we've had great experience with GLPs, and talking about the GI ill effects about smaller meals, less fatty food, and less alcohol should be emphasized at each meal to avoid the GI ill effects.

In many of the other endocrine fields, we have flexibility of dosing. In osteoporosis, we have daily pills, weekly pills, monthly pills, and every 6-month injectables and every 1-year injectables, and you choose the right patient for the right drug, and the every 6-month injectable, Prolia, has been extremely successful medication.

In the lipid field, you have daily pills. You have every 2-week evolocumab or Repatha and you have every 6-month Leqvio or inclisiran.

So the every 6-month issue has been found successful and gives physicians the flexibility of dosing, if we choose the right patient for this, whether it's a noncompliant patient; a patient who travels frequently who doesn't want to take their GLP needing refrigeration; whether it's a patient who lives half a year in the north, half a year in the South, because we have many snowbirds where we live.

So there are many instances where we could think of an every 6-month medication being very important to the public to have this kind of dose flexibility, and the FDA has had the wisdom of that in the other endocrine fields that I mentioned.

Now, in terms of efficacy, we know from the trials, the drug has efficacy, and in one of the trials as well, but in terms of some of the concerns that the FDA has, the cardiovascular safety, I'm sure like in other programs, they will

do an after marketing mega study. They're doing that with tirzepatide, or Mounjaro, now, and they did it with of the other GLPS to get that approval. In fact, oral semaglutide, or Rybelsus, is still doing a cardiovascular trial, the SOUL trial now, and I'm sure that ITCA 650 will be doing that as well. And I think we'll have positive results because it was almost positive in EXSCEL but a huge dropout rate of taking drug because of the noncompliance with the injection device.

Regarding the renal concern, all GLPS have in their package insert about acute kidney injury, and if a patient has nausea and vomiting that's uncontrolled, that you can't control it with medication, this is a drug you can get out and have removal of the device, whereas if you're on a weekly medication that has a long half-life of a week, it takes several weeks to have the drug to resolve. So here, I would feel more comfortable with this, as long as you warn the patient in the beginning about having device removal. If they had uncontrolled nausea and vomiting, you have to

call --

DR. LOW WANG: Thank you so much. I don't mean to cut you off, but we do have other open public hearing speakers --

DR. BUSCH: [Inaudible]. Thank you.

DR. LOW WANG: -- so the 3 minutes is up. Thank you so much.

Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

Yes, we are skipping directly to open public hearing speaker number 4 because number 3 is not here right now.

DR. BLEVINS: Very good. I'll start.

Is it ok to start?

DR. LOW WANG: Yes. Please go ahead.

DR. BLEVINS: Okay.

Thank you very much for allowing me to speak. My name is Tom Blevins. I'm an endocrinologist in Austin, Texas, involved in

clinical medicine and clinical research at Texas Diabetes and Endocrinology, and -- I'm supposed to start my video. [Inaudible].

DR. LOW WANG: We're not able to hear you right now. You might have to just press the microphone button.

DR. BLEVINS: I'm back. My clinic participated in one of the ITCA 650 trials. I have no financial relationship with the company, except for that trial many years ago.

This delivery device is implanted subdermally, as you know, delivers exenatide, a GLP med, for at least 6 months at a time. And you've heard this already. The practitioner can be sure that the patient's getting the medication for the entire treatment period. There are no daily or weekly injections, and patients do forget. So this is a compliance thing, and persistence, and adherence advantage.

The literature showed that the device is effective at lowering glucose and was well tolerated. The pros of using this implantable

device, with a more than 6-month effectiveness, are very clear, I think, and better compliance. You're going to hear it over and over, and I could say it five times. Better control of diabetes derives from better persistence and better compliance and effective medication, and there's really no other medicine like this. It's unique.

This medicine fills what I think is a significant unmet need in the diabetes treatment arena. It's long lasting, low maintenance need, and addresses the need for effective treatment in people who sometimes don't take their med. There are a number of studies, and I'm happy to provide references, Weiss, et al. in the UK, and the U.S. study, which was a retrospective prescription claim study, found that people with type 2 diabetes who initiated GLP-1 receptor agonist treatment, like the ones you know about -- the dailies, the weeklies, the ones we love, we do -- many of these people discontinue therapy by 24 months. In fact, in one of these retrospective prescription claim studies, 70 percent discontinued by 24 months. And

many times it was a compliance thing, or it could have been a cost thing or something like that. A 6-month device that is approved and used could make this a very different percentage.

Simply, it's my request, and for my patients treatment for choice, that you move to approve this ITCA 650. And just as a comparison, we now have an implantable glucose sensor that lasts for 6 months. People love it. They don't want to go back to their external disposable sensor. That doesn't mean that everyone's going to use it. Some people are going to; some aren't. All of these products are very effective and helpful for our people with diabetes. Thank you very much for allowing me to speak today.

DR. LOW WANG: Thank you so much.

I will now move to OPH speaker 3, so speaker number 3, please unmute and turn on your webcam. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

DR. CONNERY: Hi. My name is Dr. Lisa

Connery. I'm a board certified family physician practicing in Norman, Oklahoma, where we have a very high rate of diabetes and obesity epidemic. I've been doing clinical trials for over 18 years and an investigator on over 190 clinical trials.

Like many of the speakers here, I've experienced the many frustrations associated with trying to manage type 2 diabetes. We are so grateful that the FDA has taken such a proactive stance in approving so many new therapies but, unfortunately, based on public health data, we're not getting close to the goals that we want to. Fewer than 50 percent of the patients in the U.S. are at an A1C less than 7 percent, and it says about a third of the people have an A1C over 9 percent. So obviously, we've got to do something to change this. It's also disappointing to me to see these great results come out of clinical trials, which my patients have done extremely well in, and then it not to be reproducible in the real-world setting.

So that brings me to the main point. Among

all of these trials that I've done, ITCA 650 offers a very unique set of benefits, as you know, for compliance. I've been a principal investigator on seven of the ITCA 650 trials, from phase 2a to 3b, and enrolled about 45 of my own patients, and placed all of the mini pumps myself. They are very well tolerated. My patients did very well in this. The placement and replacement procedures are really quite easy to do in the office setting.

The results, of course, on A1C and weight loss were so impressive, but more important than statistics is the experiences of my patients. A number of them enrolled in a 4-plus year trial, so we got to see that long-term effect for them. I will never forget one of them who was an oilfield worker. He came into the trial with an A1C over 10. He had never seemed to be able to get it below 9 to 10, despite being on metformin and several other oral meds, and it was because he could not take things regularly when he was working in the oilfield. Not only did he get his A1C down to 6.9, even after he moved from Oklahoma to Texas, he

chose to come back every 6 months to get the implants done because he was so thrilled with how easy it was to do this; life-changing for this gentleman and so many of my other patients.

So as you know, this compliance issue is huge. The people that tend to benefit most from this are the people that are very poorly controlled and those that struggle with staying on treatment consistently, and they're the ones that end up carrying the highest burden, both in terms of comorbidities and cost. The thing that I find most compelling is that I still have patients asking years later, "When can I get back on that implant? That was my favorite out of all of these other meds, including the weekly injectables. That one was so easy. I want to do that again."

For these reasons, I implore you guys to consider approving this new med. I think it will literally be a game-changer for so many patients' lives and affect the well-being, worldwide, of so many of these diabetic and obese patients. Thank you so much for your consideration of my

recommendations.

DR. LOW WANG: Thank you.

Speaker number 5, please unmute and turn on your webcam. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes

MS. KUNIK: Hi. My name is Kelly Kunik. I'm a diabetes advocate, health writer, and consultant. I consulted for Intarcia in 2017, a one-time deal. I'm also a person who lives with diabetes, and I am here to represent everyone living with diabetes. I also lost two older sisters to type 1 in 1991 and 2022. My immediate family and extended family tree is filled with type 1 and type 2.

I was lucky enough to meet multiple patients with type 2 who participated in the ITCA 650 clinical trial and learned firsthand from patients themselves as they shared their ITCA 650 thoughts and experiences. What I learned blew me away and filled me with hope. I met people whose lives were

dramatically changed for the better. Their labs improved across the board. Many were able to stop taking multiple daily medications for other health but diabetes-influenced issues. All lost weight. Everyone attributed ITCA 650 as the spark for improving their physical and mental health and their lives with diabetes.

Diabetes and depression go hand in hand. Diabetes burnout is real. ITCA 650 helped the people with both. Being able to manage diabetes successfully and consistently in the long term helps alleviate financial burden of poor diabetes health in the long term. Being able to maintain a positive time-and-range A1C and more consistent favorable fasting labs helps decrease the risk of diabetes complications such as heart attacks, strokes, kidney failure, an amputation.

I'm sure you're aware that many GLP-1s, including Victoza, Byetta, Trulicity and Ozempic, used to treat type 2, initially leave people feeling nauseous for weeks, if they can get their hands on the medication. For some, nausea lingers

and never leaves. Many, including those who live alone, reported having more difficulty treating lows when using said injectables; not the case with ITCA 650.

For those who have lived decades with diabetes, a large percentage develop insulin resistance just after the 30-year mark. We also have higher rates of heart disease and scar tissue from decades of multiple daily injections. I developed insulin resistance 32 years after my type 1 diagnosis. When I attempted and finally gave up trying to use an injectable GLP-1 in conjunction with insulin pump therapy, it just didn't work, and my abdomen has 40 years worth of scar tissue, causing insulin absorption issues.

Diabetes is 24/7, 365 days a year, with no time off for good behavior, and no matter the type. ITCA 650 changed people's lives in the trial with diabetes for the better. I know that more people will benefit from ITCA 650 if given the chance. In order for that to happen, ITCA 650 needs to be given a chance. As you consider your decision

today, please consider that ITCA was the game-changer for every single person who's speaking here and who was in the trial, and can be the game-changer for everyone living with type 2 diabetes in the future. Thank you so much.

DR. LOW WANG: Thank you.

Speaker number 6, please unmute and turn on your webcam. Will speaker number 6 please begin and introduce yourself? State your name and any organization you are representing for the record. You have 3 minutes.

DR. AURORA: Hi. My name is Dr. Samir Aurora, a practicing family physician and principal investigator in Columbus, Ohio. I've been involved in clinical trials, over 200 studies over the last 20 years, in all phases of clinical trials, from 1 through 4, and a lot of the diabetes trials that have been done over the last many years.

It's been my pleasure to bring close to 40 different drugs to market on different studies, especially diabetes. I was one of the investigators for the ITCA 650 a few years ago,

5 of the 7 studies that enrolled over 50 patients in the different trials. All were done at our offices and followed closely there. And what we saw, I think, and what a lot of people here have said today, is that the biggest things that we saw was the compliance that we saw with the patients while they were on this. All 100 percent of our patients came back at regular intervals with the device in place and with significant improvements in their A1C and in their weight loss. We saw A1C improvements up to 5 percent, which no drug really had been able to do that, and I think this was primarily due to the compliance that they were getting because it was so easy for them to have this in the subdermal region.

As one of the other speakers said earlier, I still have patients that come and ask me -- who've done other trials over the years, and they said, "When can we get back on that ITCA 650?" especially because of the ease that it was and the way that they could come in. For us, too, it was always a much better thing because we were seeing them so

regularly.

That can continue to be the case, when in regular practice this is available, because these patients will come back, give us an opportunity to talk to them about their compliance, about how they're doing on the drug, check their labs, and make sure the A1C's improving, and also if they're taking other drugs that might be going on at that time.

So as we know from a lot of the data that has been talked about today, compliance runs less than 50 percent on special diabetics. A1Cs continue to be high all across our country and the rest of the world, which is, again, where something like this could be easily used in different clinics, in different offices and hospitals, and wherever it needs to be done, easily placed in.

I know there's been some concern about the renal side effects and a lot of discussion about that, and thank you to everybody who was able to share on both sides of that but, really, from my perspective, the patients are coming in regularly.

I think if us as providers are well in tune to that, if we're keeping an eye on it, and the patients are well advised on it, on the possible renal side effects, dehydration, and things like that, they can be closely monitored. We know this is a class effect. Let's try and get this approved. So thank you to everybody here for giving me the time, and I really hope that we'll be able to get this approved in the near future.

DR. LOW WANG: Thank you.

Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

MS. DELONG: Hi. My name is Rebecca Delong, and I'm not representing any organization. I'm here to talk as a type 2 diabetic myself for 24 years. I was also a clinical research coordinator in some of the earlier ITCA 650 trials. I was a participant as a patient in the phase 2 trial, where I was initially randomized to the

Byetta arm, so I had to give to myself the twice-a-day injections. Needless to say, I was very non-compliant with those.

When I started the trial, my A1C was 9. While I was on the Byetta arm, it did come down a little bit, not significantly. I think it came down to 7.8, but then after 3 months, I was able to enroll in the ITCA 650 part of the trial, where I got the device. I almost passed out every time I had to give myself an injection, but once I got the device I was randomized to that. The device was no problem when they put it in, pain free, basically.

It controlled my diabetes, my blood sugar, very well. My A1C dropped to 6.2 and stayed there while I had the device. I lost 25 pounds while I had the device. My blood pressure came down. I was able to stop taking one of my blood pressure medications during that time. My cholesterol, my triglycerides dropped from like 400 and something to under 100.

The best thing about the trial was the compliance. I had no choice but to be compliant,

but it was easy. I basically forgot I had type 2 diabetes, and I was able to just go ahead and live my life. I felt better because of the weight loss, because of the numbers coming down, and I was able to get back in the gym and exercise and be more active. The device was, like I said, pain-free when they put it in.

I also did participate as a clinical trial coordinator in the phase 3 studies. We enrolled over 50 patients at the site that I was at. All the patients were very enthusiastic about the treatment. They enjoyed the fact that it brought their A1C down with little or no side effects. I saw not very many people having nausea, vomiting, or anything else, and I didn't have any while I had the device in me either. I just think that this device with the diabetic drug is a life-changer and would change a lot of people's view and perception of diabetes and hopefully help us live longer and better lives. Thank you for your time.

DR. LOW WANG: Thank you so much.

Speaker number 8, please unmute and turn on

your webcam. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

DR. EDELMAN: Thank you, Dr. Low Wang and members of the EMDAC committee. I have no current disclosures; however, in the past, I have served on the Intarcia Scientific Advisory Board and have not received any compensation since 2018.

My name is Dr. Steve Edelman, and I've been living with diabetes for 53 years. I am founder and director of a not-for-profit organization called Taking Control of Your Diabetes, with a mission to educate and motivate people living with diabetes so that they can live healthier, happier, and more productive lives. And today, I am representing the people with type 2 diabetes whom we serve. Lastly, I'm professor of medicine at the University of California and Veteran Affairs Medical Center in San Diego.

Along with my colleague, Dr. William Polonsky, we have closely examined the issue of

type 2 diabetes medication adherence and persistence, which we feel are the most significant problems in type 2 diabetes management, limiting long-term successful therapy. Now, there are many reasons that contribute to this issue, but one key contributor is the paucity of symptoms associated with chronically elevated A1C levels, as well as with hypertension and dyslipidemia. In essence, there is little or no tangible sense of urgency.

Analyzing real-world data that we have published on and has been replicated time and time again, year after year, in multiple scientific journals, demonstrate that people with type 2 diabetes are not always filling their initial prescription, taking their medications as directed, or refilling them in a timely manner. The end result, with specific reference to weekly GLP-1s, is poor glycemic control, as well as reduced benefits from this class of agents, which include weight loss and cardiovascular risk reduction.

The issue of poor adherence and persistence in type 2 meds contribute to well over a decade of

stagnant A1C levels in the HEDIS, Medicare, and other databases, including the fact that over 30 percent of people with type 2 diabetes currently have A1C values over 9 percent. That's despite the FDA approving over 45 medications to treat this chronic condition in the past 15 years.

ITCA 650 addresses this issue of poor adherence and persistence head on, and the clinical outcomes in the real world for patients who choose this form of drug delivery, if approved, will more closely mimic what is seen in randomized clinical trials. Any company can develop the world's most effective drug for people with type 2 diabetes, but they only seem to work if they are taken. Thank you very much for your time.

DR. LOW WANG: Thank you.

Speaker number 9, please unmute and turn on your webcam. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

MS. TARANGO: Hi. Can you hear me?

DR. LOW WANG: Yes.

MS. TARANGO: My name is Esther Tarango, and I'm a type 2 diabetic. I'm not in an organization. I was a patient. In 2011, I was diagnosed with diabetes by my primary doctor and, unfortunately, the clinic that I was attending is changing primary doctors. These doctors were not much help and they didn't guide me through the disease. They introduced me to metformin, which was a medication I could not tolerate, and they kept incrementing the dosage from 500 to 2500, but since day 1, that was not working for me.

I was always irritable, weighing 198, and with very poor health issues. Plus, I'm not very good at remembering to take my medication as should be. The metformin would nauseate my stomach and make it hard for me to do my daily activities at work, as well as with the family. I was suffering, grumpy, feeling light headed, blurry vision, and breathless. My family would stay away.

But in reality, I am a happy person. I am the type of person that wakes up in the morning,

singing while cooking. I knew something had to change, so I started doing research, and that's when I was introduced to clinical trials [indiscernible] in the ITCA 650 study. I am here to tell you today that the ITCA 650 brought back the person I was. My mobility and health got better. It reduced my A1C and made it possible for me to join in family and social functions.

I call the 650 the wonder device because there are no hassles. You don't have to be changing monitors every 2 to 10 days. There are no skin irritations, it doesn't catch against your clothes, you don't have marks all over your stomach or arms, and you're able to enjoy life as you should. The 650 is a painless, small incision, not noticeable, and the device works wonders. I believe in enjoying life, and when I had the ITCA 650, I had one less worry. And it wasn't just my happiness that increased. My spouse, and children, and the people around me were happier.

I ask you today to please consider how much your decision could change my life and the life of

my family and many others out there just like me who need this kind of option to help manage their diabetes. As I said, this is one wonder device. Thank you for your cooperation.

DR. LOW WANG: Thank you.

Speaker number 10, please unmute and turn on your webcam. Will speaker number 10 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

DR. LOGAN: Thank you. My name is Doug Logan. I do not represent any organization. I have no financial relationship with Intarcia. I am a board certified internist. I practiced primary care medicine for 33 years and I spent another 11 years working as a principal investigator for clinical research studies that included seven years as a PI in a phase 1 clinical pharmacology unit. Thus, I was the PI for Intarcia's first-in-human study of ITCA 650 back in about 2009. I then served as a PI for several of their phase 2 studies, the longest such study being a 48-week

study in which we removed and inserted new devices every 3 months.

Across these several studies, between 2009 and 2013, I administered ITCA 650 to approximately 40 volunteers, and as such, I performed approximately 100 device insertions and removals. Based on my perspective as both a clinician with 33 years experience in managing type 2 diabetes and as a principal investigator who worked with ITCA 650's earlier clinical research studies, I'd like to make the following three points in support of ITCA 650.

Number one, patient compliance. This has been very well addressed by several of the clinicians and patients who have spoken before me. I would just like to reiterate that as a clinician, I have found the class of drugs just staggeringly beneficial with a triad of robust glycemic control, weight loss, and reduction in cardiovascular and renal risk. ITCA 650, as has been well described previously in this meeting, guarantees 100 compliance. Even once-a-week injections are often

met with some noncompliance.

Number two, patient acceptance. The diabetic volunteers who received active study drug in our ITCA 650 studies were uniformly very happy with both the device and the effects of the drug. Firstly, device insertions and removals were very well tolerated, essentially painless, and once inserted, the devices remained painless. Subjects usually were not even aware of their presence.

Secondly, subjects were delighted with the decrease in appetite, early satiety, and the resulting weight loss. And thirdly, they were delighted that, unlike with any other diabetic medications they've been taking, with little effort and worry on their part not having to remember to take the medication, not having to fight so hard against their own appetite to lose weight, and they were able to appreciate really impressive reductions in their daily glucose readings and, of course, eventually their A1Cs.

Thirdly --

DR. LOW WANG: Excuse me. I'm sorry. We

are at time.

DR. LOGAN: Okay.

DR. LOW WANG: Thank you so much.

Speaker number 11, please unmute and turn on your webcam. Will speaker number 11 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

DR. DENHAM: Yes. I'm Dr. Douglas Denham -- [inaudible] Texas in San Antonio. I appreciate the opportunity to speak to the committee about the ITCA 650 system. I've been a primary care doctor for 31 years, treating diabetes and all the sequelae associated with it, as well as a medical [inaudible - audio gap] researcher for the past 17.

There have been some wonderful comments from the different physicians and patients there. I would like to address one of the issues that I think astounded me the most as a provider for the past 31 years, was the emotional and psychological benefit that the patients who participated in these

trials experienced. Several of those people are going to speak today. One of them, who I think was incredibly affected by the medication and studies, unfortunately has passed away now and cannot express his feelings about it.

As a physician, over the years you've seen and tried all these medications. You try all these things to get these patients into their goals and to get their diabetes under control. It's kind of a self-defeating process for them because it's so difficult to deal with all the multiple manifestations of diabetes and the difficulties to control. With this medication and this delivery system, the compliance went up, and those things, but just the fact of the empowerment of the patients as they gain control and this feeling of not being a victim anymore [inaudible] of their disease was amazing.

One of the ladies that is a patient of mine and we've consistently seen her, she did so well with that, she referred to it as "her little baby," and it was almost hard to get her to come in to

take it out. But the psychological impact of how this drug allowed them to gain control of their diabetes, to do well, and continue on that high baseline trial for five years was amazing to me as a provider and, like I said, the psychological impact on those folks who participated. They all ask when can we get this, and we keep telling them we're waiting approval.

So in my humble opinion, I think this is a drug that needs to definitely be given a second chance and allowed to move forward. Cardiovascular and AKI issues aside, I think those were dealt with and have been dealt with during this meeting already, but as a physician and a provider for patients with diabetes, I think this is certainly a drug that I would love to have in my armamentum to help them gain control of their diabetes and of their life [inaudible]. Thanks for this opportunity. Appreciate you.

DR. LOW WANG: Thank you.

Speaker number 12 decided not to speak, so we're going to move to speaker number 13.

Speaker number 13, please unmute and turn on your webcam. Will speaker number 13 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

MR. BELTRAN: Hello. Can you hear me?

DR. LOW WANG: Yes, I can hear you.

MR. BELTRAN: Okay. My name is Ramon Beltran, and as far as who I represent, now that I think about it, I represent all the diabetics, and all the senior citizens, and the veterans. I wish they could have participated in this study, which has been known as ITCA 650.

Just a quick synopsis of how I came about to being where I am today, I was in the emergency room at Sherwood 505 [ph]. I was told my A1C was 10.5. I weighed about 192 pounds and was on an IV for about 4-and-half, 5 hours. When I was ok'd to let go, a nurse talked to me and told me about this study, the ITCA 650.

It's strange how things happen, but I've come to realize that my mom passed away at 69.

It's been a very emotional year, a very emotional year for me because my mom passed at 69, and this past June I turned 69, so needless to say, maybe it was meant to be. At that point, when I was under the ITCA 650 unit, my sugar went all the way down to 125, 155, 158, and 160 was the highest. My A1C, believe it or not, was 6.8. And now years later, my A1C is 7.7, and my sugar averages up to 185 to 155.

You find yourself in this position, you want to convince everybody. What helped me the most -- I'm going to be honest -- is the fact that I used to forget to take my meds. During that time with this unit, I never forgot because it did it for me.

DR. LOW WANG: Thank you so much. I'm sorry. We do have to move on, but thank you so much for your comments

MR. BELTRAN: Thank you.

DR. LOW WANG: Speaker number 14, please unmute and turn on your webcam. Will speaker number 14 begin and introduce yourself? Please

state your name and any organization you are representing for the record. You have 3 minutes.

MS. ROMO: Good afternoon. My name is Marie Romo. I am a diabetic. I've been for over 15 years. I have tried various pills. I would like to start by sharing a recent experience I've been going through.

On September the 6th, I received my first injection. I have never taken an injection. It was Ozempic at my doctor's office. The side effects were so crazy I felt like I was on a roller coaster, up and down. When it came down to my injection at home -- I had to administer it myself -- I wasn't sure what I was doing. The pen locked at zero, and I should have had 3 weeks more medicine.

I called my pharmacist, and she told me, "Oh, just look at YouTube, and they'll tell you how to do it." I felt so sick, and nervous, and scared, so I called the manufacturer at Ozempic, and they wrote up a safety report. I was still feeling bad. My doctor's office finally called me

hours later and said I might have taken too much at once, and scheduled me to come in, in 2 days, to see the doctor, and she added, "You should have been trained on this."

Well, saying that, the ITC 650, this tiny implant pump, is not an injection. It's not a pill. The ITC consistently delivered my medication in a steady, normal level with no interruptions for 6 months at a time. The procedure took less than 15 minutes in my doctor's office, with little to no pain whatsoever, and no training required.

When I was in the study, my A1C was 10.5 when I started the study, even though I was taking metformin. Within 2-to-3 months, my A1C went down to 7. The first time since I was diagnosed, I felt a bit of myself coming back. I had the freedom, independence, and confidence that the A1C was in control and the ITC was working for me.

I started losing weight immediately. I was energetic. I no longer thirst, and I never longer was falling everywhere. I could go the whole day without being tired. I actually went back to work.

I was living a normal life. I lived with the ITC 650 for 5 years. Eventually, the study ended, and I knew my freedom was over. I actually cried when I learned that I no longer had the ITCA 650. I honestly felt like I had lost my best friend. I felt so alone, and I knew I would not be able to be in control of my A1C anymore.

Although I've tried other options since the removal of the ITCA 650, I have not been able to regain the level of my control. I am back to a 10.5 and above. That is why I'm speaking to you today. I am sharing with you that in my experience with the ITCA, it is very safe, very easy to tolerate, and very convenient, and ensuring to people that are working hard to control their diabetes. Thank you for allowing me to explain my experience with the ITC 650.

DR. LOW WANG: Thank you so much.

Speaker number 16, please unmute and turn on your webcam. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record.

You have 3 minutes.

MS. CLOSE: Good afternoon. My name is Kelly Close. I'm president of Close Concerns. I've had diabetes for over 35 years, and I've been privileged to see so much that FDA has made happen over those years, especially in the last two decades, so thank you.

Let me start there. Thank you so much, Dr. Bumpus, for bringing us all together. Thank you, Dr. Low, advisory committee members, and FDA leaders, and the extraordinary FDA team, and everyone working in this unbelievable agency, and particularly in the Commissioner's Office, Dr. Robert Califf's office. Thank you to him.

I don't know if you know how much we appreciate the extraordinary stretch of approvals and the massive differences you have made in the lives of so many people. I've seen Marie cry. I mean, I have been with so many patients who have been so lucky to have had GLP-1 and who have had alternatives to GLP-1.

This is just the disclosures. I don't have

any financial disclosures in today's outcome. I haven't been compensated for my time or expenses. I have zero financial interest in the future outcome of this product. Two hundred-plus organizations subscribe to Closure Look. Our new service, that doesn't include the sponsor, and diaTribe, the nonprofit I founded in 2006, also has no financial interest.

GLP-1 is big. This class has soared in growth. When people take their therapy -- as TCOYD founder, Steve Edelman, said a little bit ago -- when they take it, it works, but way more people need it. It's unperfect yet. Like people like Ms. Kunik and others have stressed, a major problem is nausea. The growth is nearly vertical. It's growing especially in the U.S. Everybody watches you, so especially in innovation, we want to see more innovation, and when we don't approve of innovation, sometimes there are unintended consequences.

So I'll cut to the chase, and I'll go through the rest of the slides, but my main message

is just that the delivery consistency of GLP-1 is super important, and you can address this through postmarket surveillance. My gosh. I would love -- I mean, there have been problems. Do you want problems with consistency? There are problems with everything out there, like environmental problems, all of that. Let's keep moving the innovation and getting it to market.

It's just to say, again, the potential that this class has to address major unmet needs and address some of these barriers is huge. We believe this can really, really meaningfully reduce the management burden. That is a massive, massive deal because there are so many people who are staying alive longer because of all of the GLP-1s. We need more innovation and we need more opportunity.

You already heard that taking GLP-1 is challenging. It especially is for the most marginalized patients, so let's put a pin in that and come back to that. That is so big, what you have the chance to do. Let's keep going.

You know that greater adherence leads to

more patient benefit. We know that this is true. We've heard this today. We know that this device could meaningfully improve adherence. This is a really big deal, as you'll hear.

DR. LOW WANG: Thank you.

MS. CLOSE: Next slide.

DR. LOW WANG: Thank you so much.

MS. CLOSE: Thank you very, very much.

DR. LOW WANG: Yes. Unfortunately, we're at time. Thank you so much.

Speaker number 16, please unmute and turn on your webcam. Will speaker number 16 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

DR. ABRAMS: Good afternoon. Can you just confirm I can be heard, please?

DR. LOW WANG: Yes, I can hear you.

DR. ABRAMS: Thank you. I'm Dr. Michael Abrams, senior health researcher with Public Citizen, a consumer advocacy group in Washington DC, and we have no financial conflicts of interest

on this matter.

The analysis conducted by FDA scientists show that the ITCA 650 implantable osmotic drug pump that we've been talking about has yet to demonstrate reasonable safety that would warrant its approval as an adjunctive drug-device treatment to improve glycemic control in type 2 diabetes. The available clinical trial data has been analyzed in a variety of ways, as we've heard today, by both the sponsor and the FDA.

These analyses revealed too difficult to dispute and, we think, disqualifying characteristics about ITCA 650, at least at present. First, the device failed to deliver a consistent and predictable dose of GLP-1, the GLP-1 agonist, exenatide. Second, some subjects experienced serious adverse events, including kidney and cardiovascular toxicity. The serious adverse events were markedly more evident with the ITCA 650 use compared to placebo, another drug, sitagliptin, and even compared to general GLP-1 agonist use without the ITCA implant device.

The ITCA 650 is designed to be implanted subcutaneously, as we've heard and seen, in patients' abdomens for 3-to-6 months, without any external dosing controls; however, data from the sponsor showed that the device sometimes deliver low daily doses, 60 percent of prescribed, for example; other times, high daily doses, 180 percent of prescribed, when measured using ideal laboratory assays for such performances, which we've heard from the FDA likely underestimates the variability that we're talking about.

Moreover, separate analyses by the FDA's Center for Devices, CDRH, established that the device sometimes even fails to deliver a dose of the drug within the very wide range of 3 to 200 percent. Importantly, adverse events, some serious, are plausibly tied to this device's use. For example, acute kidney illness was evident in 1.8 percent of those implanted with the device and just 1 percent of controls, and 2 patients with acute kidney injury who received the device actually died. Separate analysis revealed that the

cardiovascular morbidity, including deaths, heart attacks, stroke, was more common with the device use. For example, 49 ITCA 650 cardiovascular deaths were observed in 32 months of follow-up compared to just 40 in placebo group.

In conclusion, the view of Public Citizen Health Research group, at this time, is that these safety concerns, combined with the manufacturing sterility concerns that have kept the drug-device, this particular drug-device, on clinical since 2017, require the FDA and this committee to reject ITCA 650, at this time, as a safe and effective --

DR. LOW WANG: Thank you.

DR. ABRAMS: -- treatment for type 2 diabetes.

DR. LOW WANG: Thank you so much for your comments.

Speaker number 17, please unmute and turn on your webcam. Will speaker number 17 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have 3 minutes.

MR. WOOD: I'm speaking together with speaker number 17B. Can she also start?

(Pause.)

17A, can you start up, please, Alison?

MS. ZENG: Hello?

MR. WOOD: Thank you.

Good afternoon, and thank you for the opportunity to present our data. My name is Richard Wood. I'm the CEO and founder of dQ&A. We're a research company specialized in diabetes. I'm presenting today with my colleague, Alison Zeng. Although we work for multiple companies in the diabetes field, dQ&A has never received revenue from Intarcia or i2o.

Since dQ&A was started 14 years ago, we've often seen how the real-world experience of a drug or device is really quite different from what happens in clinical trials, even different from what practitioners expect to see. The data we'll show you today comes from survey responses of 3-and-a-half thousand people with type 2 diabetes collected over the past few weeks, and we'll

present additional data from a special survey of a thousand people testing their likely acceptance of the ITCA 650 product.

MS. ZENG: Hi. My name is Alison Zeng. I'm a research analyst at dQ&A. I'm now going to present our research on GLP-1s and the ITCA 650. As you can see on this slide, these results compare the expectations and experiences of people who started the GLP-1 between January 2022 and June 2023. The drugs are mostly meeting expectations, but A1C outcomes are disappointing some patients. This matters because lower A1C is considered by far the most important outcome for people taking the drugs.

We also find that there's been a lot of switching between drugs in the class, and more concerningly, a substantial number of people exiting from the class altogether. Coverage issues and nausea is the biggest reason why people quit GLP-1s. In our special survey, over 1,000 people with type 2 diabetes were shown a description and image of the ITCA 650. Among those with an A1C

greater than 7, between 1 in 7 and 1 in 10 respondents said they would definitely try this option if it were approved by the FDA, recommended by their doctor, and covered by their insurance. A similar share of respondents said they would definitely not try it. Top reasons for willingness to try the products were convenience, fewer injections or pills, and fewer missed doses, which are all benefits likely to improve adherence. When we asked why people might reject the device, negative feelings towards the idea of an implant were by far the dominant reason.

In conclusion, although GLP-1s are a successful and rapidly growing drug class, they don't appear to be delivering satisfactory A1C outcomes to all the people who take them. We have seen that many people quit the class primarily due to nausea. The question then remains, what will be an effective glucose lowering therapy for this group?

Our study of the ITCA 650 concept suggests that a significant number of patients will be

willing to try it, primarily in hopes of reducing the burden of diabetes management, improving adherence, and decreasing nausea. On the other hand, negative sentiment towards the product is mainly driven by the rejection of an implantable device. Thank you again for the opportunity to present our data.

Clarifying Questions (continued)

DR. LOW WANG: Thank you so much.

The open public hearing portion of this meeting has now concluded and we will not be taking further comments from the audience. I would like to express my sincere and heartfelt thanks to our OPH speakers for sharing your experiences, thoughts, and opinions regarding today's topic.

Since we have some additional time, we'll actually take some extra time as well. We will take the remaining clarifying questions. I'd like to invite Dr. David to start us off with his question for the FDA presenters, and I'd like to remind you to state your name for the record.

DR. DAVID: Thank you for coming back to me.

I want to raise a question relating to the product that was presented just before the lunch break, if I can. And my question will have to subsets to it. The first one is, looking at the difficulty of measuring the daily dose distributed and putting that aside, what might be other factors that the FDA can identify that contribute to what we saw in slide 22, the wide variation in daily dose?

The second part of my question is I'm not sure how the product is delivered to the implantation site, but I wonder if there is premature hydration leaked into the osmotic engine that's pushing the piston before the implantation is completed. Is that a possible theory, and what can we do to mitigate that? Thank you very much.

DR. WOLLOSCHECK: Thank you, Dr. Yadin. This is Dr. David Wolloscheck. Thank you very much for your question. So regarding potential reasons for the variability that we observe in the IVR data, obviously, this is mostly speculation, but apart from difficulty with the assay, there can be difficulties with the compatibility of the drug and

the device. As I mentioned at the beginning of my presentation, this particular drug suspension is very viscous, and moving of the plunger, that point [indiscernible] to this viscous fluid can represent significant challenges for the device.

I think in addition, there could be issues with the drug formulation potentially. We know as a suspension, that does not necessarily guarantee that delivery would be even throughout the proposed study. I think other differences, when we extrapolate from that, when we think about in vivo drug delivery, I think in addition to what we observe in vitro, there could be additional variabilities introduced by things like variation in temperature, and as we discussed earlier, potential differences in the osmotic pressure.

So to summarize, I think there are lots of different reasons why the device does not deliver accurately, but ultimately, I think we would encourage Intarcia to do a root cause and to study this further. Thank you.

DR. LOW WANG: So right now, we are taking

questions from the panel for the FDA. I think that Doctor Greevy is next.

Did you have a question for the FDA?

DR. GREEVY: I did.

DR. LOW WANG: Please go ahead, Dr. Greevy.

DR. GREEVY: Okay. This is Robert Greevy. My question actually follows up on the one that was just asked and clarifies a point made earlier. Is it still possible to bring up slide 22 from the FDA slides?

On this slide, is each point in the figure a single day?

DR. WOLLOSCHECK: Yes, that is correct. Thank you.

DR. GREEVY: Okay. So on day 6, if I'm interpreting that correctly, we see that there's several days in a row, early on, on the left-hand side of the figure, where a less than expected dose is being administered; is that correct?

DR. WOLLOSCHECK: Yes, that's correct.

DR. GREEVY: Okay. And day 0, is this in the titration phase or is this during one of the

steady-state phases?

DR. WOLLOSCHECK: Day 0 would be what's referred to as the the startup phase.

DR. GREEVY: The startup phase.

DR. WOLLOSCHECK: This generally occurs with both the 20 microgram and the 60 microgram. I wasn't quite sure if you meant, with the titration phase, to go from the 20 microgram to the 60 microgram, but this is day 0, essentially, from placing the device into the saline solution.

DR. GREEVY: Okay. Thank you very much.

DR. WOLLOSCHECK: Yes. Thank you.

DR. LOW WANG: Thank you.

Do we have any other clarifying questions for the FDA? I think, Ms. Berney, if you could go ahead and unmute yourself and state your name for the record.

MS. BERNEY: My name is Barbara Berney, and I am a patient representative to the FDA. I've served on many, many panels for a number of different things, including diabetes medications. I am a type 2 diabetic. I was diagnosed in 2001,

and I've been on oral meds for years. I've been very compliant, so I guess I'm atypical, and I'm doing well. But I do have a couple of questions that might be more practicalities that nobody else has seemed to have thought about, but as a patient, I think about these things.

First of all, is there going to be training for practitioners before they start cutting up and inserting this device? Also, supposing you're diagnosed at 40 and you get this implant, and every 6 months there's an incision to implant the device, and then you come back, and they explant and implant the new one. And over the course of 40 years, a lot of us live to be older, that's a lot of tissue being disturbed. What's the consequence for scar tissue of that many attempts?

The other comment I'd like to make, I think the public speakers, they were quite eloquent. When I first heard about this, I asked people what they thought about implanting something, and I think a lot of diabetics are simply in denial. "Oh, I don't need that." Do they take their meds?

No. So there are a lot of factors here that need to be explored to be able to say, yes, it's going to be great. But the questions that I have are just things that a patient would think of. Thank you.

DR. LOW WANG: And would the FDA like to comment on those comments?

DR. ARCHDEACON: I think those are excellent comments. I appreciate them and they're very thoughtful. I wonder whether the applicant might be better positioned to address these particular questions.

MR. GRAVES: Thank you, Dr. Archdeacon. Just a real quick response to those, there would be training, insertive training, for the procedures. We also provide kits that provide everything in the kit to do any of the placement or removal procedures. And as in our phase 3 program, if the product is approved, we would not be distributing the product to anybody that's not trained and certified, so every office would need to have someone trained and certified in it to even get the

product.

The last thing about the procedures you asked about, you heard from a couple of the patients, actually, that were on our high baseline study for five years. That's multiple 6-month devices, and there were no issues. I know most of the patients in our whole program, I think it was over 98 percent of them, use the devices in the same location. The doctor would just rotate the incision on one end of the pump and put it right back in the same spot, and that was effective, and that was what most people preferred in our phase 3 study.

MS. BERNEY: Thank you.

DR. LOW WANG: Now, we'll take some time for questions from this morning for the applicant, and I ask that the panel members be brief and direct with your question. I also ask that the applicant responses be succinct. Let's go ahead and start with Dr. Crandall.

DR. CRANDALL: Sorry. I had to remember what my question was. This is Jill Crandall. I

had a question having to do with recognition of the possibility that the device was -- something that was causing the nausea and vomiting. I think this has been kind of addressed a little bit in some of the other discussion. One of the responses to mitigate the potential for kidney injury is to deal with the nausea and vomiting and volume depletion that leads to it. I think one of the first things as a clinician we do, yes, stay well hydrated, but we hold the medication for a period of time. We discontinue it or lower the dose, and that's obviously much more complicated with the implantable device.

So I'm just interested to know about how frequently the devices had to be removed, what your thoughts are about -- as stated, many patients tend to forget they have it. Will this be widely recognized as a potential cause for GI symptoms that needs to be dealt with beyond just hydration? Thank you.

MR. GRAVES: Yes. So I can respond to that. With regards to the GI side effects that happen

with GLP-1s during dose initiation and dose escalation, like we talked about this morning, when and if that happens to produce a rare AKI event on any of these drugs in the class, and you end up with a serious AKI event like the 11 patients in our one study that we've talked about, in those cases, six of the patients remained on therapy and five of the devices had to be removed.

But one of the very important, I think, practical safety features of our product is if you are on a GLP-1 and you do get a serious AKI event, which all of them produce, based on the data we showed, one of the benefits of our product is if you're there in the hospital with a serious AKI, you can get our product out, take it out, and the product will be out of your bloodstream -- I can show you data -- within 24 hours. So the product, when you take it out, the drug becomes undetectable within 24 hours. If you compare that to a patient that's on a long-acting injectable GLP-1, unfortunately, that's going to be in your body for 8 to 10 weeks when you're in the hospital with that

AKI event.

So that's the data that we know and how I would frame the context of this delivery system. If you get an AKI, at least if it's me that got that as a patient, I would want to have the option to get it out, and within 24 hours, and that's not there if you're on a long-acting GLP-1.

DR. CRANDALL: Thank you.

DR. LOW WANG: Next, I'd like to invite Dr. Wang for a question for the applicant.

DR. WANG: My question was actually answered earlier, so I have no further questions.

DR. LOW WANG: Okay. Thank you.

Then next, Dr. Nachman?

DR. NACHMAN: Sorry. I didn't have my hand up, but since you called on me, maybe I can ask a question. I have a question about how Intarcia is thinking about their post-approval CVOT trial. You did show a slide there. A very rough estimate is that it would probably take about five years for you to have a three-year follow-up on enough patients so that you could see the events that you

want.

In the last few years, we didn't talk a lot about SGLT2 inhibitors, so I'm wondering if you guys have thought about what that trial would look like. I don't want to put you on the spot in front of FDA -- I'm not with FDA -- but you must have thought a little bit more about how you would conduct that trial; how long it would take you; how many patients would you need; what would your control group be; and is it really feasible given the current climate of not only GLP-1 agonists but also SGLT2 inhibitors?

MR. GRAVES: Yes. Thanks for that question. There are, obviously, very important details for us to work out with the agency on that question, which we look forward to the opportunity to do. The slide that Dr. Sager presented, that I've got on the screen right now, gives you a high-level sense of what our objectives would be in that study. We would want to look at safety as the primary focus of that, with a secondary focus on being able to assess cardiovascular benefit. As we know from the

Kaplan-Meier curves I showed earlier in the meeting, we believe that you need to be on therapy to assess CV benefit at least 1.5 to 2 years, and probably more like 2-to-3 years. So I agree with you that the duration of the study would probably need to be a 2-and-a-half-to 3-year type duration study.

We would want to also enrich it for elderly patients and renal dysfunction that would be consistent with the labeling for exenatide, and as Dr. Sager mentioned, we would look to try to get this enrolled and completed. It all depends on how long, when we talk to the FDA, the duration of the study should be. Our view is it should be between 2 and 3 years, so that will depend on how quickly we can get it done. But that's our high-level thoughts on the trial. But there are, as you said, important details for us to work out, and that would need to be done with the agency.

DR. LOW WANG: Thank you.

I would like to try to give everyone who had a question for the applicant this morning a chance

to ask their questions, so from my list, I think we have Dr. Greevy. I don't know if you still have your question from this morning.

DR. GREEVY: I think my question's been answered since, so I'm ok. Thank you.

DR. LOW WANG: Okay. Terrific.

Let's see. Then I think, next I would like to invite --

MR. GRAVES: [Inaudible].

DR. LOW WANG: -- Dr. Weber to ask your question.

MR. GRAVES: Oh, sorry.

DR. WEBER: Thank you. This is Tom Weber, and just a question for the sponsor. I'm trying to understand the cardiovascular signal better, and one potentially plausible explanation would be glycemic variability, which is tied to both autonomic dysfunction, as well as hard outcomes, based on some recent literature. And in looking at the studies that were published on ITCA 650 in the early 20-teens, limited studies, but I didn't see any more dynamic glycemic data like glucose sensor

or other data.

I guess, do you have any data in that regard that would provide some reassurance that fluctuation in GLP-1 delivery wouldn't influence glycemic variability that could have an impact on overall outcomes?

MR. GRAVES: Sure. I would like to ask, actually, Dr. Drucker to address that, if I could.

DR. DRUCKER: Yes. Hi. As we discussed this morning, we don't have CGM data from these trials due to the historical perspective when they're done. But I think for all of the GLP-1 drugs, there's only evidence that we have a reduction in glycemic excursion. There's really no evidence that you saw this morning from the Bydureon trials for the exenatide twice daily data, where the levels of exenatide fluctuate tremendously, but we still have better glucose control. So I think it's an interesting hypothesis, but I don't think we have data to support that hypothesis with the class or with MACE [indiscernible] based medicines.

I would like to just earlier comment about the design of the trial. We do agree in this era that an active comparator design might be valuable for patients enrolling in a trial. And as noted, with respect to SGLT2, the GLP-1 receptor agonists do reduce MACE events on top of SGLT2 use, both as demonstrated in the real world and in the AMPLITUDE, other trial. So we think this is something to discuss with the FDA, but it might be in the patient's interest.

DR. WEBER: Okay. That completes my question.

DR. LOW WANG: There were two more people who had questions this morning for the applicant. One was Dr. Wilson.

Dr. Wilson, if you still have that question for the applicant, please go ahead.

DR. WILSON: Peter Wilson, Emory. I think it's a simple question for the sponsor, is what about drug-drug interactions, potentially with this product and the common medicines that our patients who are 60-years-plus are taking. Most of the side

effects were patients on metformin, ACE inhibitors, ARBs, and NSAIDs. So those plus others, is there any adverse synergy, so to speak, drug-drug interactions, that might help pave the way for more safe protocols moving forward? And I guess you might have that from Bydureon experience, just as a thought.

MR. GRAVES: Right. Since our PK data is very consistent with Bydureon, to your point just now about exenatide just given once a week versus in our extended delivery system, the drug-drug interaction studies they did, and that we also did, basically show the same results. So there's no difference, from what we know, for the same drug.

DR. WILSON: That's all.

DR. LOW WANG: I think Dr. Kalyani had a question or some data that she needed, information that she needed, from this morning for the applicant.

Dr. Kalyani, I wonder if you could maybe restate that. I don't know if the applicant was able to obtain the information.

DR. KALYANI: Yes. Rita Kalyani. It was in regards to the hypoglycemia definition and also the glycemic rescue, if they could provide more details.

MR. GRAVES: If I could have slide AA-2, please? Here we go. I won't read this slide to you, but this is directly from the protocol on the definitions that were used in the study, very standard.

Is that ok?

DR. KALYANI: Great. That's helpful. And were glucose levels monitored throughout the day or just fasting?

MR. GRAVES: Just fasting, yes.

DR. KALYANI: And then in regards to the glycemic rescue, did that occur early in the course of being on the device or at what time point?

MR. GRAVES: It was spread out throughout the trial, so there's no clear pattern of exactly when it happened, and there was more rescue on, obviously, placebo, but even in the active comparison study we did, there was more on the

comparator arms than on our product.

DR. KALYANI: Thank you.

MR. GRAVES: Thank you very much.

DR. LOW WANG: OK. So I think we have one more panel member with a question for the applicant, so, Dr. Konstam, if you could please go ahead and state your name for the record, and ask your question.

DR. KONSTAM: Marv Konstam. Thank you. I just want to return to Dr. Sager. This morning in our discussion, I had asked if you have data that compares some of the hard cardiac outcome findings to other GLP-1 agonists, other formulations of exenatide. And I just wanted to ask your interpretation of Dr. Carey's presentation, who basically gave something like I asked to us, and lined up all the studies, and showed, essentially, they all had point estimates below 1. I think she made an interesting comment about, potentially, with exenatide, maybe the baseline shouldn't be 1 because all the other formulations have reduced mortality.

I don't know if that's true or not, but can you help us? How do you interpret that? Can you see that and still have a cardiovascular-safe drug?

DR. SAGER: Philip Sager. I think the key issue here is that this study was designed under the FDA guidance and prespecified endpoints of MACE 4 intention to treat and meta-analysis to exclude what was considered unacceptable risk, a confidence interval of 1.8.

In comparing to the other studies, most of those were much larger and lasted much longer in time. The meta-analysis, which we showed you, was really consistent with the EMDAC FDA presentation back in 2018. There were 181 MACE events, so when you look here, you'd expect a hazard ratio of, potentially, in the 1.5 range and an upper confidence interval of something above 1.17; remember, this was 1.12.

So I think the problem here is comparing studies that are vastly different in terms of their sizes -- let me just bring this slide up here. This is similar to what's in the FDA's briefing

book, but the sizes of the studies in terms of the MACE events, most of them are larger. Many of them are many, many times larger, the differences in cardiovascular disease, the differences in diabetes duration. There have not been any studies that had a 1.2 or less years of follow-up that actually showed significant benefit in terms of MACE reduction.

So I think the problem here is comparing studies that, really, many of which were designed for different purposes. Most of these are post-approval trials, and they were designed to exclude confidence intervals of under 1.3. The one example we have where there was an interim analysis and a final analysis was with the ELIXA study, and I showed you how the confidence interval shrank and the point estimates also shrank.

I think what's really important here in terms of thinking about this, because of priors, is the EXSCEL study, which had almost 15,000 patients, 14,752. It had a point estimate of 0.91, and ITCA 650 is exenatide, so in terms of thinking

about biologic plausibility for harm, I think with that study, as well as all the other data, the likelihood of ITCA 650 causing harm is extremely unlikely.

Does that address your question?

DR. KONSTAM: Well, it does. I guess we'll have to agree to disagree.

DR. LOW WANG: Thank you.

I'd like to invite the FDA to make a comment on this question.

DR. ARCHDEACON: Bring that slide back up for a second, please.

DR. SAGER: I --

DR. ARCHDEACON: Thank you. If you just bring that slide up for a second, we just wanted to make a couple comments. One, the comparison here is a pooled analysis compared to the CVOTs, so the actual mean study duration for FREEDOM, which is probably the better comparison here, is 1.4 years. But in any case, it would probably not be appropriate comparing the meta-analysis to the CVOTs for this purpose.

The other thing that we'd want to comment on is that the trials that did show a benefit, it's been sort of repeated over and over again that you need long trials to see a benefit. In fact, we see an immediate separation of the Kaplan-Meier curves for MACE in all of the other trials, where there was a difference shown that was favorable. We see a separation of the Kaplan-Meier curves immediately in the other trials as well, so we don't necessarily agree that you need three or five years to see an effect. And the other thing we just wanted to say is that the FREEDOM population is certainly more similar to the populations of the CVOTs than it is to the pooled analysis.

DR. LOW WANG: Yes. Thank you so much.

DR. ARCHDEACON: Thank you.

DR. LOW WANG: I'd like to invite Dr. Everett --

DR. SAGER: Can I --

DR. LOW WANG: -- to --

DR. SAGER: -- Madam Chair, can I respond? Can I respond to that?

DR. LOW WANG: Excuse me. No. I'd like to actually invite Dr. Everett to ask his question.

DR. EVERETT: Thank you. Brendan Everett. I had a clarifying question actually on the last slide that the sponsor showed prior to that one, which showed the sample size estimates that would be required in order to exclude the upper confidence limit bound, was the slide prior to -- and there was a line drawn at about 1.5 where the sponsor argued that -- the FREEDOM set. I don't know if you can --

MR. GRAVES: Let me just pull that slide back up.

DR. EVERETT: Great. That's great. Thank you. I guess I was a little bit confused with the way that the sponsor was describing this slide. I see this as an estimate -- if you're trying to demonstrate that your product has a confidence limit that falls below that 1.8 threshold, which would prevent approval for just an indication of hemoglobin A1C lowering without having yet done a full cardiovascular outcome trial, that you could

expect a maximum point estimate of 1.26 and a confidence limit of 1.8.

What I don't think this is saying, and what I heard the sponsor to say, is that these are the point estimates that you could expect in such a trial. And, frankly, if you were to understand the effects of this product to be the same, with respect to cardiovascular outcomes, as other GLP-1s, which I think is the argument the sponsor's making, you would actually expect the point estimate to track as the others have, let's say 0.8, 0.85, even 0.9, with confidence limits that are quite broad. They may be as high as 2, and as you accumulate evidence over the course of the trial, and patients, they would then narrow, as seen in the second column of this table, from 2.0 to 1.8, to 1.5, et cetera.

So I guess I'm not quite sure what the point was of showing this slide because I wouldn't expect a beneficial drug to track with those hazard ratio point estimates, unless the effect changes over time, which I think we've seen in the Kaplan-Meier

is not the case. You would expect the point estimate to approximate what the final point estimate is going to be, just with much broader confidence limits, so it can move within that, obviously.

MR. GRAVES: Yes, and I know this is contradictory to what Dr. Archdeacon just said, but it's not true that the Kaplan-Meier curves separate immediately. You do not see benefit for any drug with durations around one year. The Kaplan-Meier curves are overlapping up and through 12 -- if you look at LEADER on the far left, there's not separation that's significant at 12 months.

DR. EVERETT: So should we be concerned that yours seem to separate in the opposite direction at about 3 months?

MR. GRAVES: It was 9-to-11 events difference. It's just underpowered to be able to make a definitive conclusion, which preapproval studies were known to be non-definitive studies because they're underpowered and they're of too short of a duration. To do the right study, we

need to do a post-approval trial so we can have duration. Something that didn't come up that's really important about our study is we had 40 percent of patients in our CVOT study that weren't even treated for 12 months, 40 percent of them. Our study was not geared to look for benefit over time; it was geared to give as many events as quickly as we could, and we had a significant portion, almost half of our population in our study, that was not even treated for a year.

So we're just comparing apples to oranges here, and I just can't emphasize that enough.

DR. EVERETT: Thank you. That's it.

DR. LOW WANG: So we are in a bit of a time crunch, so I would like to make sure that we have enough time for our last two panel members with questions, so I'd like to ask that you'd be brief in directing your question and succinct in your response.

Dr. Wang, if you could please go ahead and state your name for the record.

DR. WANG: Yes. Thomas Wang. Again, just

to actually readdress those same two points that Dr. Sager's slide shows, first, I agree with Dr. Everett that the power slide that was shown, I think the sponsor sort of misapplied that slide. I don't think the purpose of that slide was to show that as sample sizes get bigger, that a drug that is neutral or beneficial looks more favorable over time. In other words, it's just showing the scenarios of point estimate in upper limit that gets you right up to the threshold at given sample sizes, but it still doesn't alleviate the concern that a drug that -- it doesn't answer the question of how a drug that has beneficial effects might yield the observed hazard ratio and upper limit that we saw in the Intarcia drug.

Similarly, with the Kaplan-Meier curves, while it is true that a number of the other drugs had trials that had a median duration that was longer, the FDA showed a Kaplan-Meier curve, that even though the median duration of FREEDOM was 1.4 years, there was still curves that extended out to 3 or 4 years just by nature of the trial running

that long. And again, the curves, if anything, seemed to continue to diverge out to that time point, making it seem a little bit concerning that even with a lot more follow-up, that it may be hard to believe that the curves would suddenly reverse and change. But we don't know the answer, so I think we all agree that we need to find out the answer from a more definitive study.

DR. SAGER: Philip Sager. Just in quick response, the MACE 3 curve that was shown by the agency was a very blown-up curve. It went from 0 to 0.1, so it exacerbated small changes. It wasn't the primary endpoint -- that's shown here. So if you look at MACE 3 overall, maybe there's a little bit of separation later on if you look at the whole curve, but if you do blow it up, that's what was done there.

However, coming back, the point of the EMDAC from 2018 was the powering, assuming that there was equality between the two. So this finding that we have is within expectations and clearly a larger study needs to be done, but that did meet the

endpoint, the prespecified analysis. The hazard ratio was 1.12, it was far below 1.8, and thus, we would hope there would be an opportunity to explore this really post-approval. From a biologic plausibility, there's no data suggesting that GLP-1s, including exenatide in EXSCEL, have any harmful effects, so it would be very unlikely. Thank you.

DR. LOW WANG: I'd like to invite Dr. Meininger to ask your question and, again, please be brief and direct, and applicant, please be succinct.

DR. MEININGER: Sure. I think earlier in response to Dr. Archdeacon, Dr. Sager was going to say something, and he was cut off. I think it's important to just make sure he's heard. I don't know if Dr. Sager had rebutted, whatever, what Dr. Archdeacon was saying before, just to make sure that we hear all sides.

DR. SAGER: Thank you. I think the issue got covered. It really had to do with the Kaplan-Meier curves that Mr. Graves then was able

to show, so I think we're good.

DR. MEININGER: That was helpful information. Thank you.

DR. LOW WANG: I think --

MR. GRAVES: Madam Chair?

DR. LOW WANG: Oh, sorry.

MR. GRAVES: Could I have 10 or 15 seconds just to answer the PK question that was asked about Byetta and our product? Because I think it might be important for the committee just to have that data. We do have a slide on it, if I could show it real quick.

DR. LOW WANG: Go ahead.

MR. GRAVES: Thank you very much.

Someone asked earlier on the panel about Byetta, which is obviously very variable with twice daily injections; that's on the left. So that's the picograms per mL for Byetta, twice daily injections on the left. On the right is the PK data from our phase 2 study, looking at implants in phase 2 that was dose ranging. We had 10-microgram, 20-microgram, 40-microgram, and

80-microgram implants. So again, I want to be careful not to make -- with those differences in assays here, as I said earlier, so I want to be transparent. There may be assay differences here, but this does give you a relative sense of the variability with Bydureon, which I think negates a lot of the things that were presented by CDER about this variability hypothesis. We just don't see that in our efficacy or our safety data. It's less variable than this.

DR. LOW WANG: If I could just ask a quick question about this. On the left graph, we're looking at PK data over hours and on the right over days, and I'm not sure those are comparable.

MR. GRAVES: It's 2 days on the left, just to clarify. So there are 2 days of Byetta PK data there, and in our data, you can look in the 0 to 7 day range. Our devices, that's the startup period in the first part there, but that's at least 2 days on each; so it's definitely going to show you exposure for Byetta that's real.

DR. LOW WANG: Yes. I think it would be

very helpful to have that first couple of days expanded so that we could actually see the differences.

So now the FDA has their hand raised, so go ahead.

DR. ARCHDEACON: I am a little uncomfortable of us getting into a bit of a back and forth, but there are just a couple points. So one, with regards to the other CVOTs and whether the Kaplan-Meier curves separate or not, I'll just point out that HARMONY had a mean follow-up of 1.6 years and it demonstrated a benefit; PIONEER-6 had a mean follow-up of 1.3 years, and it certainly had a favorable hazard ratio. SUSTAIN-6, with a mean follow-up of 2.1 years, demonstrated a benefit; AMPLITUDE, a mean follow-up of 1.8 years. So I think it is fair to say that there is, in fact, an early separation of many of these Kaplan-Meier curves.

The other thing, I'll ask our clin-pharm colleague, Dr. Chow, to come back and address exenatide and Byetta a bit more.

DR. CHOW: Hi. This is Edwin Chow, clinical pharmacology team lead. I have several comments regarding the sponsor's PK data. First of all, the ITCA graph that was shown here, these are the phase 1 study data, where the device and the PK assay were used differently than the phase 3 data, where the exposure was much higher than what was displayed here. Second, the plot that they're showing, the Byetta plot is in hours and the ITCA plot is in days. So our argument is really the capturing and the sudden rise in the concentration, which is not able to capture for the ITCA graph.

Third is the Byetta graph, where they show higher concentration, and that is referring to mild renal impairments, which is not really comparable to what they're saying in the PK graph over here. And fourth is the drug delivery system. For Byetta, it is really a simple immediate-release formulation, where after injection, you can predict the PK variability and the PK profile of the drug, whereas the ITCA product, we have shown in vitro and in vivo that the drug release is inconsistent,

and you cannot really predict when there's going to be a large amount of drug dumped into the systemic circulation over time. So the sponsor did not really have adequate PK sampling in their program to capture these kind of sudden in-person drug concentrations. Thank you.

Questions to the Committee and Discussion

DR. LOW WANG: I think we're going to actually have to wrap up, so thanks to everyone for your comments and questions. I don't see any other questions from the committee.

So now it's finally time for the committee to turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. So we'll proceed with questions to the committee and panel discussions. I'd like to remind the public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

Let me give you an outline of the schedule.

It's about 3:40 right now. We have two discussion questions before the one voting question. We'll try to spend about 30 minutes on each of the discussion questions, and then depending on how much time we need for the discussions, we'll have a 10-minute break, and then no later than about 4:45 or so, or 4:50, we'll take the time necessary for the voting question and the vote. And at that time, we'll ask everyone on the panel for their explanation of their vote, after the vote.

If this timeline meets with your approval, let me read the first question. After I read the question, we'll pause for any questions or comments concerning the wording of the question. Our discussion question 1 is, discuss your assessment of the safety profile of ITCA 650 and whether the safety profile of the ITCA 650 drug-device combination product has been adequately characterized based on available data with respect to acute kidney injury; B, with respect to cardiovascular safety; and C, with respect to overall safety.

First of all, are there any questions about the wording of this first discussion question?

(No response.)

DR. LOW WANG: Since there are no questions or comments concerning the wording, we will now open the question to discussion.

First, I'd like to ask Dr. Newman to comment on your your thoughts about this discussion question. Go ahead.

DR. NEWMAN: Connie Newman. Thank you very much for calling on me. I'm looking at this question, the second-half asks whether the safety profile for this product has been adequately characterized based on the available data. I believe, listening to everyone today and by reading both briefing documents, that the safety profile has not been adequately characterized. We do know that there is acute kidney injury seen in the trials, as seen in other trials of GLP-1 agonists, but in the FREEDOM trial, and even in the other trials, there were very few patients who had renal dysfunction. So we only know about acute kidney

injury occurring in people who have normal renal function or maybe a mild dysfunction.

With respect to cardiovascular safety, it seems that there were many opposing views on this, and I am of the opinion that the FDA guidance from 2008 did not specifically mean that a drug was considered safe from a cardiovascular perspective if the upper limit of a confidence interval was below 1.8. And when we look at all the different analyses of the cardiovascular data, 3-point and 4-point MACE in the FREEDOM trial, we do see that the hazard ratio is always above 1, which is not the case for most of the other drugs who've had outcome trials, and that in some cases the cardiovascular outcome 95 percent confidence interval is as high as 2.

For example, in an on-treatment analysis done by the FDA for 3-point MACE, the hazard ratio was 1.36 with a confidence interval of 0.96 and the upper limit 1.92, which shows that possibly it could be neutral, but also this does not exclude a nearly 2-fold risk in cardiovascular events, so I

do believe we need more clarification of a cardiovascular safety of this product. In addition, in terms of overall safety, I think what I have said applies to that, and also, we have more adverse events in the ITCA 650 group than in the placebo groups in these trials. Thank you.

DR. LOW WANG: Thank you.

Dr. Greevy?

DR. GREEVY: Hi. This is Robert Greevy. As much as the format allows, I would definitely appreciate ping-ponging off of this idea, if possible, just because this is such a smart group and it really does help to think collectively about this.

I agreed very much that I thought CDER presented a very thoughtful analysis about the safety concerns, and I was wondering whether those concerns -- or whether the analysis, or we could see in the analysis if it would show that a lot of the risk is concentrated during what I'm thinking of as the titration phase, that process of going from 20 to 60, and maybe including a couple weeks

of being at 60; because there was talk about seeing the MACE Kaplan-Meier curves separate very quickly, which I'm wondering if we could confirm that that's occurring during this titration phase. And the sponsor presented in their analysis that it was during the initial implant phases where it seems like the AKI risk was particularly high, which is also within this titration phase.

So I wanted to ask that with a question linked to it of whether ITCA is not the right tool for when somebody's titrating; it's a better tool for when somebody's on a steady state.

DR. LOW WANG: Thank you for your comments.

I would like to call on Dr. Wang next.

DR. WANG: Thanks. I don't have an immediate response to Dr. Greevy's question, except to say that I agree that there's some plausibility in terms of the early timing with regard to any potential kidney or GI risk, and less certain about whether I would find that a plausible temporal link for cardiovascular safety.

My main comment relating to part B and

part C of this question is that I actually think that the sponsor and the FDA are in reasonable agreement on the fact that we don't have adequate data with regard to cardiovascular safety because they both agree we need another trial. The only question, the big question, is whether that trial should be preapproval or post-approval. I think to that, we get to the issue of the FDA guidance, and I agree with the comments and points that have been made earlier that the FDA guidance I don't think was intended to say if your upper limit of your confidence interval was less than 1.8, that you had to move to approval and that the safety data was ok to obtain post approval. It just provided a context for the decision making, and that context is why we have the advisory committee and other consideration.

I think that context necessarily does have to take into account that we're now 15 years later, and we have a large body of data that many medications in this drug class, and in related drug classes, are actually beneficial in terms of

cardiovascular risk; not just safe, but actually beneficial. So I think that should affect how we view the timing of when the data should be obtained, but I think everyone seems to agree that we need more data.

DR. LOW WANG: Thank you.

Dr. Konstam?

DR. KONSTAM: I think Dr. Wang got it about right. I think that, absolutely -- and again, having been there -- it was not the intent to say below 1.8 is a go-home-free card. It's necessary but not sufficient. We're deciding whether or not there is enough of a safety concern to prevent it from going to market and being open to availability to the public while this other larger trial is done. And I think to do that, I think you have to have a higher level of safety than we have here.

I think it's one thing to have an upper limit with hazard ratio of 1.5 or 1.8 if your point estimate is 0.9 or 0.85. I think it's another issue to have an upper boundary of 1.5 when your hazard ratio is 1.15 or 1.2. It's a matter of us

all using our judgment with the entirety of the data, and my judgment would be -- the question is, has it been adequately characterized? If that means that we're clear whether it's safe or harmful, no, it's not adequately characterized, but it's characterized to the point where I would have enough concern about the safety that I wouldn't want it to go to market without more clarity that there's less likelihood of harm.

DR. LOW WANG: Thank you for your comments.

Next, I'd like to ask Dr. Nason to unmute your microphone.

DR. NASON: Thanks. Martha Nason. The last two panel members actually have said most of what I was going to say. I was going to make the same points that Dr. Wang made about the general agreement that the reason these trials may not be comparable -- the sponsor has said repeatedly -- is that the other CVOT studies tend to be larger, tend to follow longer, and therefore they're not comparable but, to me, that also suggests that maybe it would be appropriate to have a larger and

longer study.

Certainly, there are some that are preapproval that are a similar size; however, those are not ones where there was a question about the estimate going in the wrong direction, and it seems like at that point perhaps -- or going substantially in the wrong direction, and it seems like at that point, there is a responsibility to rule out that potential signal of harm and make sure that is not a true signal before it is opened up, as it were, to other people who may not be tracked, may not be involved in the study, if it were to go to market, while collecting the rest of that data. So in many ways, I'm making the same point, so I'll just consider it a seconding of those other committee members' points.

DR. LOW WANG: Thank you.

Dr. Everett?

DR. EVERETT: Thank you. Brendan Everett. I think I'm in broad agreement with the comments from the previous three speakers. I think the way Dr. Wang framed it, I think we need to think about

specifically whether or not the safety profile has been adequately characterized with respect to acute kidney injury. If we accept the premise that moving forward at this point with the idea of a cardiovascular outcome trial could potentially happen post-approval, then we need to decide whether or not we think the acute kidney injury has been adequately characterized.

Safety is difficult because it's not clear that you've ever adequately characterized it. It's a challenging thing to characterize fully with trials that are really designed to show efficacy and, as such, designed with a specific and focused aim of being powered to collect a certain number of cardiovascular events; for example, at the end of the study, and the safety is what you collect along the way in a population that you think might be at risk for your areas of concern. So it's difficult sometimes because it takes a lot of patients exposed to a drug for a long time to uncover important safety risks. Others maybe are more evident a little bit earlier.

I think in this case, while I don't think that we've adequately characterized the acute kidney injury signal or safety signal, I do have serious concerns about it, and those derive both because of the signal that is there and the fact that because of the nature of the drug product, the population that's being enrolled in clinical trials -- including FREEDOM, which is the sickest, if you want to think of it that way -- have a much lower proportion of patients with significant chronic kidney disease and a lower proportion who are actively using ACE inhibitors and ARBs, which to a certain extent are kind of -- and that and metformin, those three things, are the risk factors that the sponsor has identified for the development of acute kidney injury while on the product.

Ultimately, those are the key things -- if you have fewer of those risk factors in your source population in which you're trying to estimate the risk, you're going to have a favorable estimate of risk rather than an unfavorable one. So I worry that if the drug were used in a nonclinical trial

population, that the rates of acute kidney injury would actually be somewhat higher. So I feel like while it's not adequately characterized, it's concerning. We haven't really even talked about the benefit and whether or not there's a clinical need for this product, that I think comes in the next question, but I will have to balance that against serious concerns about the kidney injury that was seen in the existing studies. Thank you.

DR. LOW WANG: Thank you.

Next, Dr. Nachman?

DR. NACHMAN: Yes. Thank you very much. Patrick Nachman, nephrology. I want to thank Dr. Everett to bring back the issue of kidney injury. In addition to the comments that he made, with which I completely agree, I think that the risk of acute kidney injury, while proportionately fairly low -- we're talking about a couple of percentage points -- it is not clear to me that we understand the mechanism. Yes, there is the association with dehydration from GI toxicity, but we also have not fully understood what prompts the

GI toxicity. Is it the excursion, the rapid excursion of exenatide? And in that respect, we don't know how those pumps function in real life if there is rapid excursion of glycemia, for example, upward, or other things that will change the environment within which that device is placed.

There's also the risk of acute kidney injury from other causes than the drug itself or other drugs. If the patient develops an acute kidney injury for whatever cause, does having the device in place exacerbate it, make it harder to control, make it harder to recognize, and deal with it in a timely fashion?

The other part that bothers me about the acute kidney injury story is the sponsor has raised the issue of concomitant risk factors, which are all things that we want our patients with type 2 diabetes to be on, ACE inhibitors in the future. I mean, more and more we're going to see SGLT2 inhibitors that can increase the risk of dehydration, by the way, and the use of diuretics is common, and I have not heard a very good plan

for how we would mitigate those risks and how we would monitor for those risks.

The FDA raised the question that what was proposed does not seem to be very adequate, but I haven't heard other comments in mitigation. So for those reasons, I don't think we have a good handle on the acute kidney injury, which should, in theory, be preventable, but I don't know how.

DR. LOW WANG: Thank you.

Next, Dr. Brittain?

DR. BRITTAIN: Yes. This is Erica Brittain. In terms of A, the acute kidney injury, I did find presentation of more systematic data that the FDA provided on this to be quite concerning, and I'm quite uncomfortable with the results we're seeing with that. I'm a little more torn about the cardiovascular because the 1.8 is prespecified, so I feel a little more uneasy about that one and concerned that these other trials may have been longer. And if it really does take a while for the benefit to kick in, then it's not really a fair comparison. On the other hand, it did sound like

there were quite a few trials that were similar length of follow-up that really did have much better results. I think it's enough to be concerning. Thank you.

DR. LOW WANG: Thank you.

I'd like to remind the panel members also if you could comment on your thoughts on overall safety, that would be terrific as well.

Next, Dr. Kalyani.

DR. KALYANI: Thanks. Rita Kalyani. When I see this question, I look at the word "adequately characterized," and I think when we look at adequately, what we're really talking about is not 100 percent certainty regarding safety, but adequate information to form the basis for approval. So when I look at A, with respect to acute kidney injury, we are clearly limited by the number of events that occurred in the population that was studied. Whether you look at on-study or on-treatment, there does seem to be a relative imbalance that does not favor being on the drug-device combo that we're discussing today.

Nonetheless, the absolute risk of acute kidney injury was relatively low in both the placebo and the treatment arms.

With respect to cardiovascular safety, again, we are limited by events in the population that was studied, and regardless of the upper limit of confidence intervals, the FDA guidance, 1.8, 1.5, 1.6, really, the point estimate of 1.2 does seem to be [indiscernible] when you look at the other GLP-1s that have been studied preapproval and look at their cardiovascular outcome trials but, to me, those two things could potentially be addressed with a well-designed, larger study, whether preapproval or post-approval, that really is designed to assess safety for those two items.

For me, the larger concern is overall safety, and we don't really have a sense of how that variability in in vitro release relates to variability with glucose excursions during the day. And the reason this is important is because we know that hypoglycemia is a tremendous safety concern. There may be people who may not have symptoms of

hypoglycemia. There could be things that could be prevented if we knew about them ahead of time. For instance, if hyperglycemia proceeds AKI through dehydration, if we could detect that ahead of time, we could prevent that adverse event.

So I recognize that at the time this trial was done, we didn't have as widespread availability of CGM, but I do think that having more information regarding glycemic excursions during the day at an individual level can better inform the safety profile to prevent these adverse events that we talked about. Thank you.

DR. LOW WANG: Great. Thank you.

Next, I'd like to ask Dr. Wilson to make your comments.

DR. WILSON: Yes. Peter Wilson at Emory. I share Dr. Nachman's concerns. You know, this happens early, the AKI risk -- that's A -- and I think you have to solve A before we can truly address B and C. I would have thought by now there might have been developed even a relatively small study that would test out a whole safety strategy

for these individuals with moderately low eGFRs and just test it out. It would be a REMS strategy of some sort just targeted for safety to get through what I call that first 4 to 5 months to avoid the serious acute kidney injuries. Somebody starts having nausea and vomiting that lasts more than a day or two, you need to call the hotline, and we need to get you seen, and then assessed, and then mitigate. So I think that's by far the biggest sticking point for me.

DR. LOW WANG: Thank you.

Next, Dr. Greevy.

DR. GREEVY: This is Robert Greevy again. I really appreciated all of the comments that have been made. One point that hasn't been made that I wanted to highlight was from the CDER presentations. They expressed some concern about these safety measures A, B, C, and it seems like they went back in turn to look really more closely at the device itself, and in turn came back with these concerns about the IVR, about the actual performance of the device. So I think that's an

interesting question because A, B, and C could potentially be investigated, both pre or post, but in terms about concerns about the device itself, if we shared those, that's clearly pre. Thanks.

DR. LOW WANG: Thank you.

Dr. Weber?

DR. WEBER: This is Tom Weber. I'm going to follow up on a question I had earlier about variability. I think Dr. Kalyani hit the nail on the head as well with regards to variation. I just want to emphasize, we're looking at a product which is different from previous GLP-1 receptor agonists. Whether they're daily or weekly, we have a measured delivery that you can be consistent with, and if we have the variability, as Dr. Greevy was suggesting, what we've seen, this is a complex molecule with complex biological effects, and I don't think we fully understand what the variation could do. So I think gathering more data would be helpful, obviously, to try to figure out that safety aspect.

DR. LOW WANG: Great. Thank you.

I don't see any other hands raised, so maybe

I can make a few comments. As member and chair of the panel, I really appreciate all the comments by committee members. In my assessment, I think the safety profile of the ITCA 650, with respect to acute kidney injury, does show a concerning safety signal, especially given the fact that the proportion of patients in the ITCA 650 trials with renal insufficiency was lower than in trials for other GLP-1 receptor agonists. I'm also concerned that we haven't really seen any information that could help us as clinicians determine when to recommend removal of the device, and some of the delayed removals and delayed, maybe, recognition of relatedness was concerning to me in some of the serious adverse events that were described.

With respect to cardiovascular safety, I wanted to echo what's already been stated by the other panel members, that the data provided demonstrates a concerning signal and should be investigated further. The latest guidance by the FDA about cardiovascular safety in diabetes drugs, it doesn't state exact cutoffs for hazard ratios,

upper limits, et cetera, but if there is a concerning signal seen in preapproval trials, then that has to be investigated further. So I think in my assessment, the signal that we see is concerning and should be investigated further.

In terms of overall safety, my main concerns really have to do with that marked intra-subject variability in the measured levels of exenatide, even at the time points that were chosen, because steady-state exposure was expected with that subsequent impact on the risk for GI adverse events and decreased renal function. So I don't think the available data for cardiovascular risks are adequate, and I think these concerns need to be addressed in further studies.

I think we do have a few more comments on this question, so I'd like to next call on Dr. Crandall.

DR. CRANDALL: Thank you. Jill Crandall. Actually, now that you've made your statements, I basically agree with all of those points. I think, for me, the combination of these concerning signals

about both renal and cardiovascular issues, combined with what we don't understand about the drug delivery and the variability of the delivery of the drug and the variability of the levels, it just seems like too much is unknown at this point. I'm actually a little surprised, given the time that's passed between the original submission for the NDA and now, that more studies weren't done to try to address some of these questions because we could certainly use more data. I think bringing together the concern and the lack of clarity about the operation of the device itself, with these somewhat unexplainable signals for renal and cardiovascular toxicity, are a big concern for me. Thank you.

DR. LOW WANG: Thank you.

Next, Dr. Burman?

DR. BURMAN: Thank you. This is Ken Burman. The presentations from both the sponsor and the FDA were excellent. There obviously are differences in their conclusions, but both are based on the existing data. It is difficult to make a

definitive conclusion regarding the data; however, the risk of AKI appears higher in patients taking the medication. The risk of cardiovascular safety, SAEs, and overall mortality may also be higher than other GLP-1 agonists. There are multiple caveats to include the patients being studied and missing data, as well as endpoints that were not predetermined necessarily. There are variations in GLP-1 levels, which tend to be relatively high, but it's unknown if they have a clinical effect and, of course, the A1C was definitely decreased.

One question is can the AKI be mitigated by clinical care and monitoring? And with regard to the overall safety, SAEs and mortality seemed increased as well. Thank you.

DR. LOW WANG: Thank you.

Ms. Berney?

MS. BERNEY: Barbara Berney. I'm your patient representative, so I'm speaking entirely from a patient point of view here and my own preference. I agree with most of what has been said about the overall safety. As far as

compliance goes, yes, it might be great for compliance and we might have a whole lot more people complying, but I can't rationalize compliance when there are so many things that we aren't sure of. We aren't sure that the overall safety has been satisfied. There are lots of things I don't really understand about this because I'm not a doctor, but I can tell you that having people take a medication just to keep them compliant might not be in the best interest of patients who do have a propensity toward cardiovascular events or kidney injury. Thanks.

DR. LOW WANG: Great. Thank you.

So it is 4:10 right now, and I think that maybe if there are no further comments about this discussion question, I'd like to summarize.

Are there any other further comments?

(No response.)

DR. LOW WANG: Okay.

There are a number of different issues we're considering here, so if you strongly disagree with the summary, please let me know. I think we had an

active discussion regarding the safety profile of ITCA 650. Starting with the first one, regarding whether the safety profile of the ITCA 650 drug-device combination product has been adequately characterized based on available data with respect to the AKI safety signal, what I heard is that panel members expressed concerns about the imbalance in AKI. Although some panel members also noted the low incidence, there were concerns expressed about this risk being increased while on metformin, or ACE inhibitors, or ARBs, which are therapies that patients with type 2 diabetes are likely to be taking.

Regarding cardiovascular safety, there were a lot of comments about this, and I think, in general, the panel expressed a lot of concerns about the point estimate of cardiovascular risk being above 1 and felt that the cardiovascular safety signal needs to be further investigated before consideration for approval.

Then lastly, in terms of overall safety, the panel did have concerns. Some of the concerns

expressed were related to, really again, AKI cardiovascular risk but also all-cause mortality was mentioned. A few panel members expressed concerns about lack of information about glycemic excursions and rate of hyper- and hypoglycemia with concerns about variability in the release of the drug.

So does anyone have any strong comments about that summary?

(No response.)

DR. LOW WANG: I think what I would like to do now is to take a quick 10-minute break, so we'll have the second discussion question after the break. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break, and we'll resume at 4:22 Eastern Time.

(Whereupon, at 4:12 p.m., a recess was taken, and meeting resumed at 4:22 p.m.)

DR. LOW WANG: Welcome back.

Now, let's move on to question 2, which is also a discussion question. I'm going to read this

question to the committee, and then I'll ask you if you have any issues or questions about the wording. The discussion question number 2 is, discuss your assessment of the benefit-risk balance of ITCA 650 for the indication to improve glycemic control in patients with type 2 diabetes mellitus.

Are there any specific questions about the wording of the second discussion question?

(No response.)

DR. LOW WANG: Okay. If there aren't any questions or comments about the wording, we'll now open the question to discussion.

(No response.)

DR. LOW WANG: There were some panel members that we didn't hear from for that first discussion question, so I would like to invite you to definitely make some comments here, if you could.

First, I'd like to call on Dr. Crandall.

DR. CRANDALL: Thank you. Yes. Jill Crandall. I think this is a really interesting question and kind of gets to the heart of this whole matter. I think the testimonials from some

of the participants in the clinical trial was very moving, and clearly there seems to be a segment of the population of people with diabetes who would really welcome this approach and have had a very positive experience with it, and I think that was very helpful to hear how strongly people feel about the benefits of this implantable device.

But I think the issue of medication adherence is complex. I found myself thinking fairly often that many of the patients with diabetes, certainly most of the ones that I see, they're on multiple medications for their diabetes, so we've solved one problem with an implantable device but that's only part of the issue. And whether people will actually come back to have the the device replaced in 6 months outside of the setting of a fairly highly motivated population in a clinical trial, I don't know. I mean, I'm not saying that I discount the potential for this kind of device, but I think we really don't know very much yet about where its place might ultimately be among the other treatments that we have available,

especially ones that are now easier to take with once-weekly injections. I think they'd really have to potentially show that adherence was better with this kind of device than with weekly injections.

One thing I wanted to mention that I didn't think to say about the issue of safety, and somewhat related to this, too, is a concern about the fact that the patient and the provider would have no feedback about device malfunction. I think that's a concern, that the only way someone would know the device wasn't working properly would be that glucose levels were increasing, and not all patients are as attentive to monitoring their glucose levels as they should be. So that's another issue related to safety that I just wanted to get on the record. Thank you.

DR. LOW WANG: Thank you so much for your comments.

Ms. Berney?

MS. BERNEY: I'm back. This is Barbara Berney. I know that the comments from -- I'm sorry, I'm losing my voice -- the public were very

moving, and I almost kind of was swayed; however, compliance consists of more than just taking your medicine. I talk to a lot of people with diabetes because this is one of the things that I'm involved in. I talk to people who tell me, "Well, I take my medicine, but my A1C isn't going down." Yes, but you're eating junk food all the time, or you're not exercising, and all of the other things that go into it. Why they are not compliant, there are a lot of factors, but what I've noticed is that they generally are compliant with taking all the other meds they take, so it's a difficult thing.

I agree with what's been said about the shortfall of evidence in the study. I think it would be very helpful to know, for all those people who did very well, whether they were compliant before. Do they have any other concomitant issues that could cause them not to be? I'm not a candidate for this at all. I mean, I have too many other things going on, but if I had a choice, 6 months for me is a long commitment to have something stuck in my body. On the other hand, I

just had 10 pieces of hardware inserted in my back.

I'm worried about people thinking, "Oh, 6 months. I won't have to do anything for 6 months," but then still not being particularly successful because they're not doing everything else they're supposed to do. So there are a lot of unanswered questions here, I think. Thanks.

DR. LOW WANG: Thank you.

Dr. Newman?

DR. NEWMAN: Connie Newman. I just wanted to say that I appreciate what the other members of the panel have just said, and I'm thinking about the benefit of this product. I believe it has been shown in the studies that there is a reduction in hemoglobin A1C, perhaps, at about 0.7 percent, although it's not clear that that's the right number. But there is a lot of talk about increased compliance with insertion of this device, but I don't think we have any data to prove that. So I wanted to know what other people think about that, whether there is data for increased compliance.

I also want to point out that when I was

looking at the some of the adverse events tables, I noticed that -- I believe it's in the FREEDOM trial, but I'm not absolutely certain it's that trial -- 17.8 percent of patients discontinued treatment prematurely, which may suggest that compliance or adherence may not be as good as we would like it to be. That's all I have to say right now. Thank you.

DR. LOW WANG: Thanks for those comments.

The only way that I can think of, in terms of these data on adherence, which we don't have specifically, we do have participant discontinuation from the treatment and from the trials, and it's still fairly high in these trials; 15 to 20 percent I think is what I saw, and then I think it was a bit higher in the patients on ITCA 650. But I think that because the patients on placebo were also getting devices implanted, that could actually underestimate the difference. So I think that more data on adherence would be helpful because I'm not convinced that even though hypothetically it seems like it should be great to

be able to take something once every 6 months, so far it hasn't really panned out in the data that were demonstrated.

Next, Dr. Munir.

DR. MUNIR: Kashif Munir. I too thank the people who spoke up, and the patients who have used the drug, and even the investigators who have also had an opportunity to use this, and that's what made this very tough because it does seem like it could have a great benefit for definitely a subset of the population with diabetes. I guess as far as risk-benefit, there's definitely a benefit, and I think we see A1C lowering and we see weight loss, but we do have other options, and we do have drugs that can possibly supersede this drug-device combination in A1C lowering, and definitely in weight loss, it looks like, from the data that's been presented, although not head to head.

I think it comes down to this risk that we've kind of discussed. I know the FDA and the sponsor had a little bit different interpretation, even including different patients, specifically for

the renal risk and excluding some on the sponsor side and including those. But even if you take that data, which I agree with, maybe those patients shouldn't be included in the renal analysis because it didn't seem like the acute kidney injury was related to the drug, but even if you include that, there's still a higher risk, and then the cardiovascular risk I think is really unclear.

Then I guess the last point is the adherence part. If this drug fluctuation is really true, they showed exenatide Byetta, the short-acting formulation, but those drug peaks are occurring simultaneously with meal intake, so there is a little bit more predictability, as long as you're taking the drug correctly, that when those peaks are happening at the time you want to increase insulin secretion and incretin, effect might be beneficial, whereas in this case, it seems like the peaks of drug would be random and not necessarily related to food.

The other issue is if you really are getting low drug delivery on some days, or no drug

delivery, then the adherence point that I was trying to make before is that if you're not getting any drug, it's essentially being nonadherent to your medicine even though you weren't trying to do that, but it would be essentially equivalent. So I agree there's no data, but then, also, if there are these wide fluctuations, that might also lead to an unintended nonadherence to the medication. So overall, I think there are a lot of risks still that we have to kind of work through, and the benefits probably don't outweigh those at this point with the data we have. Thank you.

DR. LOW WANG: Thank you.

Dr. Kalyani?

DR. KALYANI: Thanks. I just want to say that it's clear that there is potentially a huge benefit for any new therapy for diabetes to be introduced into the market. As we heard, the numbers continue to grow. We have many therapies, but many patients with diabetes are clearly not meeting their goals, so this innovative route of delivering the medicine is noteworthy. So I want

to thank the sponsor, the colleagues, and many patients and advocacy groups that spoke today because I think that it's truly a very compelling reason to to carefully consider this drug-device combination.

I think it's important to remind ourselves that this drug-device combination does demonstrate glycemic benefits and weight loss benefits on par with the other GLP-1s that are on the market, and that's important to notice. It has the potential to improve medication-taking behavior, and no doubt, on an individual level, as we've heard from some patients who were in the trials, it was truly a game-changer. I think the question is whether on a population level there's adequate data to demonstrate safety that everyone who wants to take this could actually take it in a safe way, and I wish there was more data in an objective way to support that medication-taking behavior was improved or was similar to available injectable and even oral GLP-1s that are on the market. But again, thanks again for all the presentations

today.

DR. LOW WANG: Thank you.

Dr. Cooke?

DR. COOKE: In terms of the benefit, I do clearly see that this medication lowers the hemoglobin A1C and presumably has the long-term microvascular benefits of that. It had relatively modest weight loss benefits, but as been said, there are other medications available that can do the same and maybe do additional things of having cardiovascular benefit; that certainly there isn't a suggestion of that occurring with this medication, at least with the current data.

I agree with the others who have said that the adherence issue is still a little bit uncertain, but I don't doubt that there is a subset of patients for whom the twice-a-year placement benefit in terms of adherence will be important to get the benefits that this drug-device combination can give; however, in order for an individual patient to make that decision about whether that benefit-risk balance of what the benefit can

deliver, and the improvement in adherence that the patient might be able to get out of this compared to the risk, they have to know what the other risks are. That's where I think the earlier discussion of just not having a firm idea of what the risk of AKI and the impact on cardiovascular disease is just makes it impossible to make that decision, even on a patient-by-patient basis.

So I think, ultimately, there's likely going to be a place for this medication, or something very similar to this, but it would need to be with more complete information about that risk.

DR. LOW WANG: Thank you.

Next, Dr. Wang.

DR. WANG: Thanks. I've spoken previously about the risk, and I still think that that is really the --

DR. LOW WANG: I'm sorry. If you could please state your name, that would be awesome.

DR. WANG: Sorry. Thomas Wang. I've spoken previously about the risk, which I think is really the pivotal issue when it comes to the voting

question, but I just wanted to make a comment about the benefit. It's clear that compared to placebo, this drug does lower hemoglobin A1C and lower weight. When we talk further, though, about the benefits of adherence, I think it's necessary then to consider that the real question we want to answer is how this delivery mechanism is better than the alternatives, either weekly injectables, daily injectables, or even now the pill that we have. So as the sponsor and the FDA consider how future data might be gathered to answer some of the questions that have been raised, I would ask them to consider what the appropriate control for that would be. Thanks.

DR. LOW WANG: Thank you.

Dr. Everett?

DR. EVERETT: Thank you. Brendan Everett. Just quickly, I agree with what Dr. Wang said. I think there's a clear benefit here with respect to hemoglobin A1C lowering and modest weight reduction, but a few years ago, when many of us in this group sat on a panel convened by the FDA to

think about how to revise the 2008 guidance, a lot of the conversation in the room, including coming directly from some of the patient representatives on that panel, were that our focus on hemoglobin A1C, and even ASCVD events -- so MACE -- was too narrow and didn't provide the patient a broad enough sense of what the potential benefits and risks were. And I think that that perspective played a significant role in the modification of the guidelines from 2008 to the present ones for approval of new drugs for diabetes. In particular, I think kidney disease and kidney function in patients with diabetes has really come to the fore as a fundamental and critically important consideration, in addition to the traditional ASCVD outcomes, like heart attack and stroke. But on top of that, I think heart failure, as well, and atrial fibrillation are other areas where we see potential benefits for existing medications.

So if that's the landscape where you're considering and comparing an unmet clinical need for a drug that lowers hemoglobin A1C by, let's

say, 1 percent versus competitors, which maybe has to be administered weekly instead of every 6 months, but has benefits potentially on heart failure, benefits on cardiovascular outcomes, and benefits on kidney outcomes, the sliver of unmet clinical need and the benefit is awfully thin to counterbalance what we don't know and what signals we are seeing with respect to risk. So I think the benefit-risk balance is just not there for this drug-product combination, ITCA 650. Thank you.

DR. LOW WANG: Thank you.

Dr. Brittain?

DR. BRITTAIN: This is Erica Brittain. Yes. I basically agree with everything that's been said, and there seems to be a lot of consensus. I also wanted to particularly agree, though, with the comment that Dr. Wang made about the future study. As much as I normally love placebo-controlled trials, maybe this is a situation of really focusing on the question of what the effect of the different dose delivery systems is, given there seems to be pretty good understanding of how well

the injection drugs do in terms of safety and so forth. So I think this might be a case where I would think that that might be the right design instead of placebo controlled, which, like I say, I rarely would think that. Thanks.

DR. LOW WANG: Thank you.

I don't see anyone else with raised hands, so maybe I can make my comments right now. I agree with what the panel has said and really appreciate your critical comments. I appreciate the speakers at the open public hearing. I really felt like that was extremely moving, hearing testimonials about how beneficial this has been in their lives during the clinical trials. I appreciate the FDA comments, the applicant's comments.

When we're thinking about this balance of benefits and risks of a therapy -- this particular therapy we're thinking about A1C lowering, weight loss, potential improved adherence -- I think that the A1C lowering that was demonstrated was modest and the weight loss was modest. There is really no evidence for improved adherence, and I think there

are some problems that are highlighted in the briefing document related to the device itself, some instances where imaging had to be done in order to find the device and then referrals to interventional radiology or surgery to remove the device, so I think it's not that simple. In terms of risks, the safety concerns really haven't been characterized adequately yet, and these signals for increased AKI and cardiovascular risk I think are there. So I think that the overall balance is unfavorable for ITCA 650.

Does anyone have any other comments they'd like to make for this discussion question?

DR. KONSTAM: It's Marv Konstam. I just want to say, first of all, I really enjoyed everybody's comments, and I really was moved by the patients. I think they're crying out for something that will make their lives better, and it's very appropriate for them to do so. To me, that doesn't weigh against the decision to approve it or not if we have residual serious safety concerns and, in fact, we'd be doing them and the public a

disservice to have this be the device that leads the way in this modality of drug delivery and turn out that it does harm. I think we're really better off going back to the drawing board, and there may be other devices under exploration, and maybe the company wants to dig deeper into this and do more preapproval work. But I think when it comes to this type of device, I think we should approve something that's safe and effective.

DR. LOW WANG: Thank you for those comments.

Let me try to summarize. As with my previous summary, please, additional comments from the panel members on this are appreciated. Regarding the panel's assessment of the benefit-risk balance of ITCA 650 for the indication to improve glycemic control in patients with type 2 diabetes, what I heard was that, in general, panel members felt that the benefits of ITCA 650 didn't outweigh the risks. Panel members commented on the moving testimonies during the open public hearing. Type 2 diabetes is a devastating disorder to live with. We need to do better with available

therapies and other treatments, but right now there are other options for type 2 diabetes treatment, and several of them reduce cardiovascular risk and risk for kidney outcomes.

Furthermore, I heard the panel members talk about adherence being a very complex problem, and the management of type 2 diabetes is not just about taking a single medication; there are many other factors. Right now, we really don't have evidence for improved adherence or adequate data to alleviate the safety concerns. The benefit of A1C lowering is not enough for a type 2 diabetes medication necessarily now; we need to also be looking at cardiovascular benefits, heart failure, and kidney outcomes, among others.

Any further comments on that summary?

(No response.)

DR. LOW WANG: Okay.

From the FDA's standpoint, is there anything we haven't mentioned that you think is important to discuss further?

DR. ARCHDEACON: Thank you. The discussion

has been excellent. No, we have no further questions at this time.

DR. LOW WANG: Okay. So I think we're on time, so now we'll proceed to question 3, which is our voting question for today. Commander Latoya Bonner will provide the instructions for voting.

CDR BONNER: Thank you, Dr. Low Wang. LaToya Bonner, DFO. Question 3 is a voting question. Voting members will use the Zoom platform to submit their votes for this meeting. If you're not a voting member, you will be moved to a breakout room while we conduct the vote. After the chairperson reads the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that the voting will begin.

A voting window will appear where you can submit your vote. There will be no discussion during the voting session. You should select a vote in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote. Once all

voting members have selected their vote, I will announce that the vote is closed. Please note there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the list and each voting member will state their name and their vote into the record. Voting members should also address any subparts of the voting question, including the rationale of their vote.

Are there any questions about the voting process before we begin?

(No response.)

CDR BONNER: Since there are no questions, I will hand the meeting back over to the chair.

DR. LOW WANG: Thank you.

Now I'll read the voting question, and then ask whether or not you have any specific questions about the wording. Here is the voting question.

Based on the available data, has the

applicant demonstrated that the benefits of the ITCA 650 drug-device combination product outweigh its risks for the treatment of type 2 diabetes? If you vote yes, please explain your rationale. If you vote no, please also explain your rationale, and then comment on additional data that could be provided to demonstrate the benefits outweigh the risks.

Are there any specific questions about the wording of the voting question?

(No response.)

DR. LOW WANG: Okay. It looks like there are no questions or comments about the wording of the question, so I'll turn the meeting back over to Commander Bonner so that we can begin the voting on question 3.

CDR BONNER: We will now move non-voting participants in the breakout room.

(Voting.)

CDR BONNER: LaToya Bonner, DFO. Voting has closed and is now complete. The voting results will be displayed.

(Pause.)

CDR BONNER: LaToya Bonner, DFO. I will read the vote results into the record. For vote question number 3, zero yeses, 19 noes, zero abstentions. I will now turn this meeting back to our chair.

Dr. Low Wang?

DR. LOW WANG: Thank you.

Now we'll go down the list and have everyone who voted state their name and vote into the record. Voting members should also address the subparts of the voting question, including the rationale for the vote.

We'll start with Dr. Newman.

DR. NEWMAN: Connie Newman. My vote was no, and that is because of the lack of understanding of the safety profile of this drug. I'm particularly concerned about the possibility of cardiovascular harm for which there was a signal in the FREEDOM trial, and I'm also concerned about the need for a greater understanding of acute kidney injury. What I think could be done would be more data, perhaps a

premarket, large cardiovascular outcomes trial that is appropriately powered and could possibly include to also assess acute kidney injury. I think it would be helpful to have more data on patients with modest kidney disease, if that is possible. Thank you.

DR. LOW WANG: Thank you. Next is me. My name is Cecilia Low Wang, and I voted no. I was concerned about the inconsistent and wide variability in both the in vitro studies under ideal conditions, as well as the pharmacokinetics studies, which I did not find reassuring. I think these concerns need to be resolved since the level of variability with some of the very high peaks and low nadirs were likely impacting the risk for adverse GI effects and the subsequent risk for acute kidney injury. I'm concerned that the data presented, which show an imbalance in acute kidney injury, as well as that cardiovascular safety signal, need to be resolved.

In terms of additional data that could be provided, I think many of the panel members have

mentioned some possible ideas for the trials, but I think that we need more robust collection of adverse renal events, and then I think we need to be looking at the cardiovascular risk signal more closely.

Next, Dr. Konstam?

DR. KONSTAM: Yes. Marv Konstam. I voted no. I guess approved diabetes drugs is a two-part process. The first can yield initial approval if there is evidence of efficacy in glycemic control and if there is minimal or no active concern about safety so that we can send the drug to market with the understanding that there will be a postmarketing cardiovascular outcome trial. I think that's the idea, and I think the upper boundary 1.8 is tied up in assuring ourselves that there's no concern. In this case, I think every issue raised by the FDA is well supported. There seems to be a lot of variability in delivery. There seems to be an excess of AKI compared to what's expected, and there is a concerning signal for excess cardiovascular outcomes.

I'll just say that the folks who testified here deserve something along the lines that they're asking for. It's a signal to industry that they may be on to something, to this company, that they're on to something, and now it behooves industry to provide all of them with a solution to what they're asking for, about which we're confident is safe and effective.

DR. LOW WANG: Thank you.

Dr. Crandall?

DR. CRANDALL: Yes. This is Jill Crandall, and I voted no. I think, as the others, it was the the signal of the adverse renal and cardiovascular outcomes, plus the lack of clarity about the device and the variability of the drug delivery that really impacted my decision. I think those two issues outweigh the potential benefit at this point. In terms of what additional data, of course, like we all have been saying, I think there needs to be a larger cardiovascular outcome trial with more close attention paid to renal outcomes and consideration of an active comparator in this

trial, potentially even something like Bydureon, which is the same medication but in a different delivery system.

DR. LOW WANG: Thank you.

Next, Dr. Nachman?

DR. NACHMAN: Yes. Patrick Nachman. So I voted no, and I don't want to repeat what my colleagues have said. What has swayed my vote is, with respect to the acute kidney injury risk, I do recognize that the absolute risk is low, and I do believe in my heart that there should be a way to mitigate it, to prevent it, to treat it quickly, but the time to figure out how to mitigate the risk is before approval, not afterwards. So I would have felt much more confident if we had a clear path to mitigating the risk.

With respect to the CVOT study, I have real reservation as to what a postmarketing CVOT study would be and how long it would take to complete, especially with all the other drugs that are currently available and have proven that benefit, that are available on the market. Thank you.

DR. LOW WANG: Thank you.

Dr. Cooke?

DR. COOKE: This is David Cooke. I voted no. I voted no because the uncertainty of the risk in terms of AKI and impact on cardiovascular outcome is too much to outweigh the possibility of benefit gained from the adherence issue and, as we've discussed, is not even that well defined.

I think in terms of what I feel is necessary to achieve approval, I feel very strongly that the question surrounding the AKI needs to be clarified before approval, and that would best be assessed through a comparator, an active comparator. I would recommend that it be another GLP-1 agonist, and I think showing, as the sponsor is hypothesizing, that the impact on AKI of this treatment is no different than that of any other GLP-1 agonist needs to be proven.

I do agree that the issue of the impact on cardiovascular outcome needs to be clarified. To me, given the very small numbers of events that were picked up in the sponsor's trial, it really

leads to such a large uncertainty of where the point estimate is, and that I think it would not be inappropriate to be done as a postmarketing study; although, obviously, it would also be nice to have it premarketing or preapproval, but I think the CVOT could be post-approval.

DR. LOW WANG: Thank you.

Next, Dr. Burman?

DR. BURMAN: Thank you. Ken Burman. I voted no. There are potential benefits to include decreasing A1C, and perhaps patients in compliance would be improved, but the disadvantages of potential renal disease, cardiovascular disease, and GI problems outweigh the benefits. I agree with the postmarketing study, which should have predefined kidney markers and AKI and cardiac endpoints. It should measure GLP-1 levels daily, and on some occasions perhaps throughout the day to get better variation.

GLP-1 agonists should be measured as accurately as possible, and perhaps that's HPLC. Of course, we would assess A1C, weight, GI

endpoints, and correlate the symptoms with GLP-1 agonists, and assess creatinine levels frequently. I agree with the slide that said the study should study elderly patients, patients with renal failure, and increased cardiovascular risk should be 2-to-3 years long, should use a CGM, and have an active comparator. Thank you.

DR. LOW WANG: Thank you.

Ms. Berney?

MS. BERNEY: I voted no for all the same reasons that the rest of the panel members have voiced, and especially I would really like to see some evidence of how compliant and how much it benefits. Also, I wasn't particularly excited by the amount of reduction in A1C, which I guess if you're a 10, 7 seems very good. But there are just too many unanswered questions for me to feel comfortable endorsing this. But I really do have to say I was very moved by those who spoke up in the public section. It seems like it could be a life-changer for a lot of people, if they could give us the data to properly assess all of the

questions. Thank you.

DR. LOW WANG: Thank you.

Dr. Wilson?

DR. WILSON: Peter Wilson. I voted no. As I think about this safety study, which I think I agree, especially with Dr. Nachman and others who have been talking about it, I think that needs to happen first. I think that could be a fairly short duration study, and it may be advantageous to figure out the best mitigation protocol to reduce adverse kidney effects before undertaking a CVOT.

So the sweet spot I think is individuals 45 to 75 eGFR, mLs per minute for the BSA, and patients probably not on insulin because that's really the target group for this molecule and this delivery. And then some other considerations that have been mentioned in some of the discussions, some subgroups with CGM with continuous glucose monitoring, more data with drug levels, especially during the course of the trial and perhaps at the time of an AKI event, and also complete case reporting with acidosis and tracking creatinine, as

mentioned by Dr. Burman. Thank you.

DR. LOW WANG: Thank you.

Dr. David?

DR. DAVID: Thank you, Dr. Wang. I was impressed by the remarks during the public comments from the users and from the clinician who prescribed the device and participated in the studies. I recognize that there is a lack of sufficient data relating to the safety, and that was the main reason that I voted no.

I think that there is variability in the delivery of exenatide and we need to be able to see the impact in hours, not in days. I think that we need to see an in vivo, in addition to in vitro, study to determine a possible connection with the AKI signal that were shown by different outcomes. There is also a need for a study to determine how a patient, as well as a clinician, can determine that the pump is not functioning, the osmotic mini pump is not functioning, as intended, and what is the signal that maybe needs to be removed and explanted. Being in the body, there are a variety

of environmental conditions, all the way from now, in the summer, being on the beach and exposed to sun and skin temperature rising that can impact the performance of such pump, and we need to have a study to demonstrate the variety of environmental conditions are understood as far as their impact on the delivery of the drug. I concur with other comments that were made by other panelists. Thank you.

DR. LOW WANG: Thank you.

Next is Dr. Kalyani.

DR. KALYANI: Thanks. Rita Kalyani. I voted no. As a clinician and endocrinologist, I fully recognize the need for innovative and new routes of administration to improve medication-taking behavior and reduce the burden of managing diabetes for people with diabetes. The uncertainties regarding renal and cardiovascular risks identified in the studies presented to date could potentially be addressed with larger trials specifically designed to systematically assess these risks; however, the great degree of

variability regarding the in vitro release of the drug and lack of a stop-guard mechanism to immediately turn off the drug-device in case of a dangerously high or low drug level raises potential safety concerns.

Without a monitoring plan to assess malfunction of the device when used by the patient, safety cannot be assured and risks outweigh benefits. This could be addressed by conducting studies that provide evidence regarding glycemic excursions throughout the day or a requirement to use CGM in conjunction with the device that could alert the user to potential concerns with the exenatide drug-device combination in real time and might subsequently prevent the development of adverse events. Thank you.

DR. LOW WANG: Thank you.

Next, Dr. Kagan?

DR. KAGAN: This is Leonid Kagan. I voted no. The FDA and the sponsor are in agreement about primary endpoints, showing that this drug-device combination showed as efficacious; however,

additional potential endpoints could be added in future studies. The device has great potential to improve adherence; however, such improvement wasn't demonstrated yet and, again, should be demonstrated in the future.

However, the major concern is that the risk is not predictable. It's different from other studies. Mechanism of toxicity and concentration toxicity relationships are not well characterized, and these taken together, with unstable release rates that were shown and significant variability in concentrations with the patient, clearly indicate to me that additional studies, starting from demonstrating release rates, and further case samplings are needed. Thank you.

DR. LOW WANG: Thank you.

Next, Dr. Weber?

DR. WEBER: Tom Weber. I voted no. While there is clearly need to improve adherence to anti-diabetes therapies, I don't feel that ITCA 650 met the benefit-risk threshold for FDA approval, given the variability in delivery and systemic

levels potentially, and that those may be linked to an increase in renal GI and CV safety signals.

I think we need more clinical data and, I think, to better characterize the potential glycemic variation by means of CGM or other methods, as well as perhaps a short-term trial, as has been mentioned before, specifically looking at renal effects and ways to mitigate that would be helpful to help foster potential future approval of the drug.

DR. LOW WANG: Thank you.

Dr. Munir?

DR. MUNIR: Kashif Munir. I voted no. I pretty much echo a lot of what people have already said. I do agree that the renal risk is there. Whether other drugs in this class also have that, it seems like they may, but it does seem that it would be advisable or beneficial to have more data on that. The cardiovascular outcomes, unfortunately it's a small study and not many events, but the numbers kind of fell on the wrong side of the fence for the sponsor, unfortunately,

so I do think they need to complete that. I guess the big question is before or after approval, and I'm still on the fence on that.

I think the thing that I wanted to stress, and I know some people mentioned this, is the clinical day-to-day data as well. I do think something like CGM to get a better sense of whether drug levels are truly fluctuating that much or is it just a measurement issue that the sponsor stated might be the cause for some of that. And I know the PK data also don't fully support that, but I think it would be nice to have CGM to match with drug levels to see if the drug levels are really low on a particular day or time and whether or not we see glycemic excursions. I also think a really good adverse events log, daily adverse events log, as well, to see if patients when they're spiking levels, potentially, whether or not that leads to more GI adverse events specifically, or other things as well, would be important. Thank you.

DR. LOW WANG: Thank you.

Next we have Dr. Nason.

DR. NASON: Thank you. I'm Martha Nason. I voted no. I want to take a moment to add my thanks to the public speakers. I thought they really motivated very well the need for longer treatment options and made that very clear. Unfortunately, it would, of course, be a disservice to those patients to move forward with the device-drug combination that was not safe, and I just don't think we have that answer yet. I don't think we can be confident anyway

So, like my colleagues, I think we need clinical data, more clinical data. I think we need a better understanding of safety and the variabilities in concentration. I agree with an active control trial, and I wanted to add that one thing the sponsor could then take advantage of was really targeting the population to focus on those with a history of compliance challenges to other modalities, injectables, whatever the options are for them, in order to, in that focused population, show evidence of benefit on adherence and what the clinical implications were of that.

DR. LOW WANG: Thank you.

Next, Dr. Wang?

DR. WANG: Thanks. Thomas Wang. I voted no. I appreciate this innovative approach that's been developed, delivering important therapy that might address unmet needs in diabetes care. That said, I feel that we do need more data to assess the benefit-risk balance prior to approval. Given the uncertainties about safety, I think the best setting for these data is in a preapproval setting rather than post-approval. While I see the benefits of shorter-term trials focused on specific renal and pharmacokinetic questions, ultimately, I come to the unavoidable conclusion that a larger and more definitive cardiovascular outcomes study is necessary to address both renal and cardiovascular safety, and it would be best to do that in a preapproval setting. I also believe that the option of an active comparator should be strongly considered. Thank you.

DR. LOW WANG: Thank you.

Dr. Brittain?

DR. BRITTAIN: I'm Erica Brittain. I voted no. It was not a totally easy decision for me because, again, as everyone talked about, the moving statements from the people in the public hearing was part of it and, again, the cardiovascular trial did meet the prespecified rule, and I do think that means something. However, like everyone has said, this just seems too much uncertainty about safety on multiple fronts.

I do think as far as the cardiovascular study going forward, I already said earlier, I really favor the active control. I have to say I'm not a hundred percent convinced about that. I think that's something that does need some consideration about the pros and cons of that versus placebo, because then, now we're talking about a noninferiority trial, and we have to have a margin, and all that. However, I still think I probably would end up feeling like the noninferiority trial is getting at the actual question of what the delivery is doing because

you're comparing the same drug but different delivery systems, and is probably the right way to go. But there should be some careful consideration of the pros and cons of placebo control versus active. Thank you.

DR. LOW WANG: Thank you.

Dr. Greevy?

DR. GREEVY: This is Robert Greevy. I also voted no for the same cost benefit reasons that have been mentioned. The device itself seems to have, I think, great, great potential. I think if operating at a very good level, I could really see it as a game-changer. I'm also not convinced, given the data we were presented, that we've seen the best version of this device. There appears to be evidence that the dispensing of the medication is not consistent, and we didn't see any data to explain why that could be or to convince us that it's not the case.

For example, the timing of this osmotic pump really depends on the conditions that are changing within the body or is variable within a person, so

the timing of the dispensing becomes more random; or is it that the amount of medication getting dispensed, due to the viscosity of the material that it's contained, results in some randomness being induced due to how it comes out? It certainly does seem persuasive that over a sufficiently large amount of time those changes balance out, but the concern is in the short time frames, either that day or series of days, where you're getting a very different dose than what's expected, and what are the complications of that.

I think, preapproval, that can really be investigated. Even in vitro, I think there's data to be collected in terms of getting a better understanding of the timing of the releasing and the quantity of the releasing of these particular pumps, and potentially even address some of those questions about differences in blood composition and how those interact with this osmotic pump. I think there can be things learned there. I'd really like to see that done prior to another in-person study because I think it's worth

considering the fact that the reason that we really want to see more in-person data is because there's some evidence of harm, so we have to be really thoughtful about when does it make sense to go ahead and do that in-person study.

In terms of efficacy, I was a hundred percent persuaded by the efficacy of the medication. I thought there was strong evidence. Even with the missing data, I thought the evidence was very strong. So I'm not super compelled in wanting to see more efficacy data; I just want to see more safety data.

I am not at all convinced that, either in practice or for a study, we should be discovering somebody's GLP-1 RA tolerability with an implanted device. If I was going to have my druthers, the way I would want to design a safety study is I would want to have everybody titrate up on something like Byetta, and only after we've established tolerability of these GLP-1 RAs at a sufficiently clinical dose, then we randomize to potentially either to just continue on Byetta or

using the ITCA 650. And something like that I feel would be a really apples-to-apples comparison, and we would get past this issue of tolerability, where it seems like a lot of the problems are occurring, both in practice and in the study, and I'm not sure that's where we really want to be putting a lot of effort into trying to understand a problem that really ought to be fixed by practice instead. Thank you.

DR. LOW WANG: Thank you.

Dr. Everett?

DR. EVERETT: Thank you. This is Brendan Everett. I voted no. I think many of the others on the call have already elucidated my rationale and, of course, you heard it from me earlier in the conversation. But I think I agree with Dr. Low Wang, that the variability in the device function could potentially be critical to both the GI intolerance and subsequent AKI issues. I think that that's really the key signal of risk that I couldn't really get by in terms of agreeing to approve the drug prior to doing a more rigorous

study, both of kidney injury and potential cardiovascular safety, so I think that the outcomes trials need to be done before marketing approval.

I do remain concerned for the cardiovascular outcome and would, of course, be thrilled if, in a larger trial of longer duration, our concerns could be assuaged and we'd see a risk estimate of 0.9 just like the longer acting, once-weekly injectable formulation of this medication. However, we don't have those data and we don't know that to be true yet. So I think that whatever program the FDA and the company agree to move forward should be a cardiovascular outcomes trial that is specifically focused with the prespecified renal outcome as well, and I think the renal outcomes that we're seeing are not GFR slope or changes in GFR over time, but rather these episodic events, where people get sick, and even if it's superseding a gastrointestinal infection that leads to a fair bit of nausea and acute kidney injury, those kinds of events need to be ascertained prospectively and actively, and then rigorously adjudicated by an

independent endpoints committee of kidney specialists.

So I think designing those aspects of the trial, prior to starting the trial, will be key, and I think it's likely that if it's done correctly, that we'll have a really solid answer about whether or not there is, in fact, any renal risks associated with this drug and its method of delivery, specifically.

I agree with the others this method of delivery is really enticing. I think if it can be done safely, I think that this would be really favored by certainly many of my patients who would love to take one fewer pills or administer one less self-injection. So I think that there's a lot of opportunity here and, of course, we heard that in the public comment section as well. So with that, I'll stop, and thank you.

DR. LOW WANG: Thank you all so much.

Let me summarize the committee's comments. As you heard, none of the panel members voted yes and all 19 panel members voted no. What I heard is

that panel members mentioned the uncertainty about AKI and cardiovascular safety, as well as the variability in drug delivery being the greatest concerns, and then whether or not this is the best version of the device was questioned. Additional studies suggested included a cardiovascular and renal outcomes trial with rigorous adjudication of key endpoints using an active comparator, especially with Bydureon or another GLP-1 receptor agonist, and then really studying more patients with more severe renal disease. There was mention of maybe a GFR range of 45 to 75 and also including older adults with diabetes; so more information about GLP-1 receptor agonist levels; more complete case reporting of adverse events of interest; assessment of adherence; and then continuous glucose monitoring were mentioned, and that last one to assess glycemic variability.

One panel member suggested doing a trial that included a run-in with an injected GLP-1 receptor agonist to select the patients who tolerate this therapy before implanting the

device-drug combination, and then a postmarketing study was mentioned by a few panel members for cardiovascular safety, as well as kidney safety.

I think, overall, the panel acknowledged the work that has gone into ITCA 650 and this innovative approach, but felt that it would be a disservice to our patients to recommend approval with the safety and drug delivery concerns that exist, and panel members voiced their understanding of the negative impact of type 2 diabetes and the hope that the applicant can do these additional safety studies because of the great potential for this device.

I think we're at the end now, and I'd like to express my deep appreciation for the work that went into preparing for and organizing this meeting by Commander Bonner and the staff at the FDA. I thank all of the panel members for your time, your expertise, meticulous attention, and the robust discussions that we had. I'd like to thank the applicant and the FDA for your concise and informative presentations, and I'd like to thank

the individuals who spoke during the open public hearing for your important contributions to this meeting, and lastly, the members of the public for attending.

So before we adjourn, are there any last comments from the FDA?

(No response.)

Adjournment

DR. LOW WANG: Okay. I don't see any, so we will now adjourn the meeting. Thank you.

(Whereupon, at 5:32 p.m., the meeting was adjourned.)