FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC) MEETING

Thursday, October 31, 2024

8:30 a.m. to 5:05 p.m.

Meeting Roster

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Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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Clinician-Scientist, CPC Clinical Research

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Professor and Chair of Medicine

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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

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. LOW WANG: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking, and also a reminder to everyone to please silence your cell phones, your smartphones, and any other device if you have not already done so. For the media and the press, the FDA press contact is April Grant. Her email is currently displayed.

My name is Dr. Cecilia Low Wang, and I will be chairing this meeting. I will now call the October 31, 2024 Endocrinologic and Metabolic Drugs Advisory Committee meeting to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. We'll start with the FDA to my left and go around the table.

DR. YANOFF: Good morning. Dr. Lisa Yanoff.

DR. ARCHDEACON: Good morning. Patrick Archdeacon, Deputy Director, Division of Diabetes,

Lipid Disorders, and Obesity.

DR. PENZENSTADLER: Good morning. Justin Penzenstadler. I'm a clinical team leader in the Division of Diabetes, Lipid Disorders, and Obesity.

DR. SUZUKI: Mari Suzuki. I'm a clinical reviewer in the Division of Diabetes, Lipid Disorders, and Obesity.

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

DR. ROY-CHAUDHURY: Good morning. Prabir Roy-Chaudhury. I'm a nephrologist at the University of North Carolina at Chapel Hill and the Co-Director of the UNC Kidney Center.

DR. CHRISCHILLES: Good morning. I'm Elizabeth Chrischilles. I'm from the University of Iowa, Department of Epidemiology, and I am the chair of that department.

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

Metabolism.

DR. ONUMAH: Good morning. Barbara Onumah. I'm a practicing adult endocrinologist in Largo, Maryland.

DR. DRAKE: Matthew Drake. I'm an adult endocrinologist and associate professor of medicine at the Mayo Clinic in Rochester, Minnesota.

DR. LOW WANG: Good morning. My name is Dr. Cecilia Low Wang. I'm a Professor of Medicine and endocrinologist at University of Colorado.

DR. FRIMPONG: Good morning. Joyce Frimpong, Designated Federal Officer, FDA.

DR. WANG: Thomas Wang. I'm a cardiologist and Chair of Medicine at the University of Texas Southwestern.

DR. EVERETT: Good morning. I'm Brendan Everett. I'm a cardiologist at the Brigham and Women's Hospital in Boston and Associate Professor at Harvard Medical School.

DR. KONSTAM: Marv Konstam from the Cardiovascular Center at Tufts Medical Center and Professor of Medicine and Radiology at Tufts

University School of Medicine.

MR. TIBBITS: Paul Tibbits, patient representative.

DR. NASON: Good morning. I'm Martha Nason. I'm a mathematical statistician at the National Institute of Allergy and Infectious Disease, NIH.

DR. SHOBEN: I'm Abby Shoben. I'm a biostatistician at The Ohio State University.

DR. PARSA: Afshin Parsa, adult nephrologist and program director at the NIH.

DR. SELIGER: Steve Seliger, adult nephrologist and epidemiologist at University of Maryland School of Medicine.

DR. IRONY: Ilan Irony, endocrinologist. I work at Johnson & Johnson Innovative Medicine, and I serve as an industry representative for the meeting.

DR. LOW WANG: Thank you all, and welcome.

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.

Now, Dr. Frimpong will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. FRIMPONG: 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 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 the 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 services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential 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 new drug application 210934 for sotagliflozin oral tablet submitted by Lexicon Pharmaceuticals, Incorporated, for the proposed indication as an

adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus and chronic kidney disease. This is a particular matters meeting during which specific matters related to Lexicon Pharmaceuticals' new drug application 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 the FDA's invited industry representative, we would like to disclose that Dr. Ilan Irony is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Irony's role at this meeting is to represent industry in general and not any particular company. Dr. Irony is

employed by Johnson & Johnson.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committees of any financial relationships that they may have with the firm at issue. Thank you.

DR. LOW WANG: Thank you, Dr. Frimpong.

We will now proceed with the FDA introductory remarks by Dr. Patrick Archdeacon.

FDA Introductory Remarks - Patrick Archdeacon

DR. ARCHDEACON: Thank you.

Good morning. My name is Patrick Archdeacon. I'm the Deputy Director of the Division of Diabetes, Lipid Disorders, and Obesity. I'd like to thank everyone for participating in today's advisory committee meeting, especially

those people who are living with type 1 diabetes. I also want to thank the members of the EMDAC for sharing with FDA their perspectives on the resubmission of NDA 210934, sotagliflozin to improve glycemic control in adults with type 1 diabetes and chronic kidney disease.

Type 1 diabetes is characterized by the destruction of pancreatic beta cells, usually leading to severe insulin deficiency. Around 2 million Americans live with type 1 diabetes. The advent of insulin therapies significantly reduced the acute morbidity and mortality associated with type 1 diabetes, and the Diabetes Control and Complications Trial demonstrated that optimizing glycemic control lowers the long-term risk of microvascular complications.

Chronic kidney disease, or CKD, is a progressive condition characterized by structural and functional changes to the kidney. CKD is present in 20 to 40 percent of patients with diabetes. It typically presents in patients with type 1 diabetes only after a disease duration of

5 to 15 years. In late stages of CKD, kidney and non-kidney complications develop, including cardiovascular disease.

Optimizing glycemic control is a primary focus in the management of type 1 diabetes. Pramlintide, a synthetic analog of human amylin, is approved as an adjunct to insulin therapy; however, insulin and insulin analogs remain the mainstay of pharmacotherapies to improve glycemic control. Some devices like continuous glucose monitors and hybrid closed-loop pumps have been shown to further improve glycemic control; however, with current treatment options, fewer than one-quarter of adult patients with type 1 diabetes achieve recommended glycemic targets.

Captopril was approved by FDA in 1993 for the treatment of diabetic nephropathy in patients with type 1 diabetes and proteinuria. No other products were approved by FDA to slow the progression of CKD in patients with type 1 diabetes until the submission of the DAPA-CKD and EMPA-Kidney trials. These studies evaluated

dapagliflozin and empagliflozin, respectively, in patients with type 2 diabetes and chronic kidney disease, and in patients with chronic kidney disease without diabetes. They did exclude patients with type 1 diabetes and CKD.

For both dapagliflozin and empagliflozin, FDA determined that the demonstrated benefits apply to patients with CKD and not just patients with type 2 diabetes and CKD. This then includes patients with type 1 diabetes and CKD. Although FDA-approved labeling for these products do not include a limitation of use recommending against the treatment of CKD in patients with type 1 diabetes, they do include a limitation of use recommending against their use to improve glycemic control in patients with type 1 diabetes. Notwithstanding the FDA approvals, treatment guidelines published by professional societies have yet to recommend either dapagliflozin or empagliflozin for use in patients with type 1 diabetes and chronic kidney disease.

A commentary published last year in Lancet

Endocrinology called attention to the lack of new therapies for patients with chronic kidney disease and type 1 diabetes, despite the emergence of new therapies for patients with chronic kidney disease and type 2 diabetes or non-diabetic CKD.

A figure from the piece reproduced here omits the clinical trials of dapagliflozin and empagliflozin, which were the basis for the recent FDA approvals. The figure also omits a trial of sotagliflozin conducted in patients with CKD and type 2 diabetes, SCORED, and a trial of semaglutide conducted in patients with chronic kidney disease and type 2 diabetes, FLOW.

Nonetheless, it highlights the striking difference in the number of clinical trials conducted in people with type 1 diabetes and CKD compared to those conducted in people with type 2 diabetes and chronic kidney disease and in people with chronic kidney disease without diabetes.

The study authors acknowledged challenges in studying chronic kidney disease in patients with type 1 diabetes, while also asserting that the

entire community -- clinicians, professional and patient organizations, funding agencies, the pharmaceutical industry, and regulators -- need to do more to address the lack of proven effective treatments.

Addressing the challenges of evaluating new therapies for patients with type 1 diabetes and chronic kidney disease requires that we find the appropriate balance between the need for timely access and the need for evidence of safety and effectiveness.

FDA has convened this advisory committee to discuss the benefits and risks of sotagliflozin, another SGLT inhibitor, for a proposed indication as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes and CKD. For purposes of this application, the applicant has defined CKD as an estimated glomerular filtration rate, or eGFR, of 45 to less than 60 milliliters per minute per 1.73 meters squared, or eGFR greater than or equal to 60 and a urine albumin creatinine ratio, or UACR, greater

than or equal to 30 milligrams per gram.

NDA 210934 was initially submitted in 2018 seeking the following indication. Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus. The original submission was not approved because FDA determined that the increased risk of diabetic ketoacidosis, a life-threatening medical emergency, outweighed the benefits in patients with type 1 diabetes.

In 2022, FDA approved sotagliflozin as Inpefa to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure or adults with type 2 diabetes, chronic kidney disease, and other cardiovascular risk factors. The basis for the approval was two large cardiorenal outcome trials.

SCORED was a trial conducted in adult patients with type 2 diabetes, moderate to severe chronic kidney disease, and other cardiovascular risk factors. SOLOIST was a trial conducted in

adult patients with type 2 diabetes and heart failure. The indication granted by FDA encompassed all adults with heart failure irrespective of diabetes status; however, the applicant did not propose, and FDA did not consider, an indication that would encompass all patients with diabetes mellitus, chronic kidney disease, and other risk factors.

In the current resubmission, the applicant asserts that, 1) the effect of sotagliflozin on A1C can be expected to be similar in patients with type 1 diabetes and chronic kidney disease compared to patients with type 1 diabetes without chronic kidney disease; 2) patients with type 1 diabetes and chronic kidney disease accrue greater benefit for the same reduction in A1C compared to patients with type 1 diabetes without chronic kidney disease; 3) the increased risk of DKA associated with sotagliflozin can be expected to be similar in patients with type 1 diabetes and chronic kidney disease compared to patients with type 1 diabetes without chronic kidney disease; and 4) data from

patients with type 2 diabetes suggest that patients with type 1 diabetes and chronic kidney disease may experience additional non-glycemic benefits.

After the presentations by the applicant and the FDA, and after the open public hearing, we'll ask the committee to discuss the following points to help FDA evaluate whether the applicant's assertions are justified.

Discussion point number 1, discuss the evidence and uncertainties based on the existing clinical trial data that sotagliflozin improves A1C across a range of eGFRs, including the following categories: 45 to less than 60, 60 to 90, and greater than 90. Consider the durability of the treatment effect demonstrated.

Discussion point number 2, discuss the evidence and uncertainties that patients with type 1 diabetes and CKD accrue a greater benefit with respect to microvascular disease than patients with type 1 diabetes without CKD for any given reduction in A1C. In your discussion, consider different KDIGO categories of CKD classified by

both eGFR, 45 to less than 60, 60 to 90, and greater than 90, and UACR, less than 30, 30 to less than 300, and greater than or equal to 300. Discuss the magnitude of clinical benefit conferred by the A1C reductions expected with use of sotagliflozin across a range of CKD severity, considering both eGFR and proteinuria.

Discussion point number 3, discuss whether the magnitude of a DKA risk in patients with type 1 diabetes and chronic kidney disease has been sufficiently characterized. Discuss the evidence and uncertainties regarding DKA risk for patients with type 1 diabetes and eGFRs in the following ranges, 45 to less than 60, 60 to 90, and greater than or equal to 90.

Discussion point number 4, discuss your view of the scientific rationale justifying extrapolation of the demonstrated benefit of sotagliflozin to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in patients with type 2 diabetes, moderate to severe CKD, and other

cardiovascular risk factors to patients with type 1 diabetes and mild to moderate CKD.

Discussion point number 5, discuss other potential benefits of sotagliflozin suggested by SCORED. Discuss your view of the scientific rationale justifying extrapolation of such potential benefits to patients with type 1 diabetes and mild to moderate CKD.

Discussion point number 6, discuss the overall benefit-risk assessment for sotagliflozin as an adjunct to insulin to improve glycemic control in patients with type 1 diabetes and eGFR 45 to 60, or eGFR greater than or equal to 60 and a UACR greater than or equal to 30. Address how to consider the increased risk of DKA relative to the benefit of an A1C improvement in the population proposed by the applicant. Discuss how you weigh other advantages of sotagliflozin in the benefit-risk assessment for the proposed indication.

After consideration of the points for discussion, we will ask the committee to vote on

the following question. Do the available data demonstrate that the benefits outweigh the risks for the indication of improved glycemic control in a population of patients with type 1 diabetes and an eGFR 45 to less than 60 or eGFR greater than or equal to 60 and UACR greater than or equal to 30?

If yes, provide your rationale and suggest specific risk mitigation approaches. If no, do the data demonstrate that the benefits outweigh the risks for the indication of improved glycemic control for another population of patients with type 1 diabetes and CKD defined by different eGFR and/or UACR categories? Explain and clarify the population in which the benefits of improved glycemic control outweigh the risks, if any. Thank you.

DR. LOW WANG: Thank you, Dr. Archdeacon.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure that such transparency at the advisory committee meeting is present, the FDA believes that

it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including industry's non-employee presenters, to advise the committee of any financial relationships that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest in a sponsor, 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 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.

Let's now proceed with Lexicon Pharmaceuticals' presentation.

Applicant Presentation - Brian Corrigan

MR. CORRIGAN: Chair, members of the committee, FDA colleagues, good morning. My name is Brian Corrigan, Senior Vice President of

Regulatory and Quality Assurance at Lexicon Pharmaceuticals. Thank you for the opportunity to present the data and analyses demonstrating how sotagliflozin fills an important unmet medical need, and does so with a positive benefit-risk profile, as an adjunct therapy to insulin for patients with both type 1 diabetes mellitus, T1D, and chronic kidney disease, CKD.

For people with type 1 diabetes, insulin therapy is a necessary and life-saving intervention. Unfortunately, despite advances in insulin formulations, delivery methods, and management, only 20 percent of patients with T1D achieve adequate glycemic control. Without effective glycemic control in the target range that limits either hypo or hyperglycemia, patients with T1D experience greater morbidity and remain at risk of complications, including cardiovascular disease, progression to end-stage kidney disease, and mortality.

Lexicon developed sotagliflozin as an adjunct to insulin to improve glycemic control in

patients with type 1 diabetes. Sotagliflozin is an oral anti-hyperglycemic drug that lowers blood glucose through mechanisms complementary and independent to insulin. Sotagliflozin works as a dual inhibitor of the sodium glucose co-transporter 1 and 2, referred to as SGLT1 and SGLT2. By inhibiting SGLT1, sotagliflozin blunts and delays intestinal glucose absorption and reduces postprandial glucose excursions. By inhibiting SGLT2, sotagliflozin reduces renal glucose reabsorption and increases urinary glucose excretion.

The clinical development program for sotagliflozin includes three phase 3 studies that enrolled nearly 3,000 adults with type 1 diabetes. It remains to this day the largest phase 3 program for an adjunct to insulin in type 1 diabetes. In all three studies, sotagliflozin demonstrated statistically significant benefits compared to placebo across the primary and most predefined secondary endpoints.

Evidence from each of the three studies

demonstrate that the addition of sotagliflozin to insulin therapy improves glycemic control compared to placebo in the overall population of patients with type 1 diabetes. These benefits were consistent across all prespecified subgroups, including baseline demographics and disease characteristics.

The 2019 EMDAC meeting, there is acceptance that sotagliflozin is effective, as demonstrated by the consistent evidence from the three phase 3 studies. As previously noted, each of these studies showed statistically significant improvements in glycemic control, as well as effects on clinically relevant secondary endpoints, all without an increase in severe hypoglycemic events.

However, we also observed an increased occurrence of diabetic ketoacidosis, or DKA, compared to placebo, though the total number of events was small. Based on this evidence, the committee was split, voting 8 to 8 on the benefit-risk of sotagliflozin in the overall

population of patients with type 1 diabetes.

Despite the acknowledged substantial evidence of effectiveness for A1C reduction, Lexicon received a complete response letter in March of 2019. The agency concluded that the benefit-risk assessment was not favorable based on concerns about the increased risk of DKA in the sotagliflozin-treated study participants.

During follow-up discussions with the FDA, in December 2023, we proposed pursuing the identification of a subpopulation of T1D patients from the phase 3 program that either gained additional benefits or had diminished risks. The FDA indicated that it would review a resubmission based on this proposed approach.

In another formal interaction in March of this year, the FDA indicated that the rationale we provided for our revised indication, that improved glycemic control may confer greater benefit to patients with T1D and CKD than to patients with T1D without CKD, was a reasonable approach for the NDA resubmission.

Since the CRL, we also completed the SCORED study. The SCORED study provided long-term evidence that sotagliflozin use results in heart failure and CKD benefits, both of which reduce clinically important morbidity events. SCORED is a multicenter, randomized, double-blind, placebo-controlled phase 3 study in more than 10,500 patients with type 2 diabetes, chronic kidney disease, and other cardiovascular risk factors. These results contributed to the approval of sotagliflozin in 2023 via a different NDA under the brand name Inpefa for a heart failure indication.

The SCORED results reinforced our belief that sotagliflozin could have potential long-term benefits beyond A1C control alone; specifically that sotagliflozin could reduce CV and CKD complications and death in patients with type 1 diabetes and chronic kidney disease.

Now, to provide some additional context on the greater unmet need in this patient group, published evidence, including data from the

Diabetes Control and Complications Trial, has established that CKD in the setting of diabetes is associated with a greater need for glycemic control in controlling for CKD risks. That is because CKD itself is an independent predictor of accelerated disease progression and increased morbidity and mortality.

Poor glycemic control contributes to eGFR decline and more rapid progression to end-stage kidney disease. This progressive eGFR decline increases the risk for heart failure. Further, decreased time in range elevates the risk for kidney complications. And finally, these patients are at an increased risk of death compared to a population without CKD.

Patients with type 1 diabetes and CKD represent a high-risk subset with significant unmet medical need who would gain additional benefits from improved glycemic control. In identifying an appropriate subgroup of CKD patients, Lexicon proposed a CKD definition based on consensus scientific standards from the Kidney Disease

Improving Global Outcomes, or KDIGO, group, which recognizes both eGFR and albuminuria as independent risk factors in predicting kidney disease progression and other comorbidities.

Lexicon utilized these criteria in identifying a population of CKD patients that both captured a spectrum of disease progression and aligned with the study criteria for the phase 3 program. Throughout today's presentation, we will refer to this population as the T1D-CKD subgroup.

The FDA used a different CKD subgrouping strategy based on eGFR levels regardless of albuminuria, which is also an accepted and scientifically justified approach to identifying a range of CKD progression to best assess in which subpopulation sotagliflozin may present the most favorable benefit-risk profile.

As you've seen in the data presented in our briefing package, the FDA's briefing package, and in what we will share today, we acknowledge that there is uncertainty in the group of patients with an eGFR of less than 60, where the near-term

efficacy and safety profile of sotagliflozin is not as robust when compared to the CKD population in earlier stages of renal impairment; however, we selected this subgroup to maintain consistency with KDIGO group guidelines and in recognition of the significant unmet need these patients have for improved glycemic control. It is the population that could achieve the most potential long-term benefits in the form of CV and kidney risk reduction.

To address these uncertainties, in our presentation today, we will also share results from the FDA identified subpopulation of patients with an eGFR range of greater than or equal to 60 and less than 90, which perhaps best balances the need to identify a higher risk population that demonstrates clinically important glycemic control coupled with a safety profile similar to the overall phase 3 T1D population. We'll refer to this population throughout our presentation as the eGFR 60 to 90 subgroup.

We acknowledge this was not the specific CKD

population we originally defined, as it was not part of the scientific consensus standard we utilized as our guide, but we credit the FDA with identifying a group that represents another subpopulation within our phase 3 program with high unmet need, without the uncertainties attributable to patients with an eGFR less than 60. As such, we will be showing you data today from both our T1D-CKD subgroup, as well as this eGFR 60 to 90 subgroup.

As a reminder, the original NDA for sotagliflozin was for use as an adjunct to insulin in the overall population of patients with type 1 diabetes. After a split 8-8 vote at the 2019 EMDAC, the FDA determined that the risk of DKA outweighed the benefits. We are here today targeting a high-risk subpopulation of T1D patients with CKD who will gain additional benefits from a similar level of glycemic control seen in the overall T1D population.

There does remain an increased risk of DKA, and that will always be present in this class of

drugs, but these patients also face other significant health consequences from advancing disease and may be willing to accept a therapeutic option with an increased risk of DKA for the near-term glycemic control benefits, weight loss, level 2 hypoglycemia reductions, and potential longer term benefits of reduced CV risk and renal progression.

However, we acknowledge the uncertainties outlined in FDA's briefing document in patients with an eGFR less than 60. To that end, we are highlighting a potential alternative subgroup based on the FDA's analysis of the phase 3 program that removes the uncertainties of the less than 60 population while retaining a mild to moderate risk CKD population that is still in significant need of therapeutic options to help manage glycemic control and slow renal disease progression. Both of these subpopulations reflect the real unmet medical need for new adjunct therapies to insulin and represent an improved benefit-risk profile compared to the overall population of T1D patients.

When applying the T1D-CKD and eGFR 60 to 90 subgroups to the overall phase 3 data set, we see that those represent interpretable subpopulations from which to base an assessment of the efficacy and safety profile of sotagliflozin. The eGFR 60 to 90 subgroup reflects an even larger subpopulation of patients from our phase 3 program, nearly 50 percent of the entire T1D study population.

Because our phase 3 studies were all statistically significant on the primary endpoint and demonstrated consistent benefit across all prespecified subgroups, we can reliably assess CKD patients who have an even greater unmet need. The primary evidence we are presenting includes 458 patients from the T1D subgroup of whom 274 received sotagliflozin, and 1,386 patients in the 60 to 90 subgroup of whom 841 received sotagliflozin. Based on this evidence, we are proposing to indicate sotagliflozin as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes and chronic kidney

disease. The recommended starting dose is 200 milligrams of sotagliflozin once daily before the first meal of the day.

With that background in mind, here is the agenda for the remainder of our presentation. We welcome your consideration and discussion of both the T1D-CKD and eGFR 60 to 90 subgroups as potential pathways to bringing sotagliflozin to T1D patients who have a significant unmet medical need. We have additional experts with us today to help address your questions. All outside experts have been compensated for their time and travel to today's meeting. Thank you. I'll now turn the presentation to Dr. Edelman.

Applicant Presentation - Steven Edelman

DR. EDELMAN: Thank you, and good morning. My name is Steve Edelman. In addition to serving as Professor of Medicine in the Division of Endocrinology, Diabetes, and Metabolism at the University of California San Diego and Veteran Affairs Medical Center, I'm also a person who has been living with type 1 diabetes since my early

teens, over 50 years ago.

I am also the Founder and Director of a not-for-profit organization called Taking Control of Your Diabetes, which is dedicated to educating and motivating people living with diabetes and their loved ones. I have focused my career on new diabetes treatment, research and education to help people with diabetes live healthier and happier lives. I'm happy to be here with you today to discuss the need for a new oral adjunct therapy to insulin for patients with type 1 diabetes and chronic kidney disease that will improve their glycemic control and help diminish the long-term complications associated with diabetes.

People with type 1 diabetes face significantly higher risk of morbidity and mortality. In the United States, an estimated 1.7 million adults have type 1 diabetes with approximately 21 percent, or 360,000, also affected by chronic kidney disease. Without effective glycemic control and other important preventative measures, patients with type 1 diabetes are at a

10 times higher risk of cardiovascular disease; a 6-fold greater risk of progression to end-stage kidney disease; a 4 times greater risk of heart failure; and a 2 to 5 times greater risk of all-cause mortality.

In addition, CKD itself is a recognized independent predictor of the increased morbidity and mortality, so CKD adds to the risk from type 1 diabetes. These data underscore the critical importance for targeted interventions that treat this high-risk subset of patients.

Despite advances in insulin therapy and glucose monitoring, most patients with type 1 diabetes do not meet glycemic control targets with insulin alone. It is estimated that only 20 percent achieve an A1C of less than 7 percent and about 50 percent have an A1C greater than 8 percent. Patients who do not achieve A1C targets remain at significantly greater risk of complications associated with their condition.

While poor glycemic control is known to increase the risk of diabetic kidney disease,

recent evidence highlights the impact of kidney function decline in individuals with established kidney disease. The three-year Preventing Early Renal Loss, or PERL study, was a multinational, placebo-controlled study designed to evaluate kidney outcomes in patients with type 1 diabetes and established kidney disease receiving allopurinol.

Although allopurinol did not have an effect, important information came out of this study. The authors found that a higher baseline A1C, as shown by the different colored shapes, was linked to a higher risk of progression to end-stage kidney disease and increased eGFR decline.

Additionally, the study showed that baseline albumin excretion rate modified the relationship between A1C and eGFR, resulting in more pronounced kidney function decline. Thus, the PERL study provided evidence demonstrating that glycemic control is a major determinant of eGFR decline among individuals with type 1 diabetes and established kidney disease.

There's also compelling evidence supporting the link between kidney function decline and increasing albuminuria on the risk for hospitalization for heart failure in patients with type 1 diabetes. In this retrospective study from Sweden, the authors investigated the excess risk of heart failure in over 33,000 patients with type 1 diabetes followed for approximately 8 years. Increases in albuminuria were associated with a higher risk of heart failure.

Specifically, patients with macroalbuminuria over 300 milligrams per gram had a 5-fold increase in heart failure risk. We also see progressively increasing risk as eGFR progresses from mild, to moderate, to severe kidney impairment. These findings support that both albuminuria and declines in eGFR are independent risk factors for heart failure in patients with type 1 diabetes.

Diabetes management aims to reduce the risk of cardiovascular disease; kidney failure; retinopathy; neuropathy; and other complications, in part, by improving glycemic control while

minimizing the risk of hypoglycemia. Our goal is to help patients achieve the guideline recommended target of an A1C below 7 percent and improve their time in range, which represents an established metric that translates into clinically meaningful benefits for patients. By achieving glycemic control, we can stabilize kidney function, mitigate long-term disease progression, and reduce the significant morbidity and mortality that the cardiorenal burden puts on patients with type 1 diabetes and kidney disease.

Current treatment approaches for type 1 diabetes and CKD also emphasize lifestyle interventions, including lowering excessive body weight and blood pressure. Challenges with current treatments impact patients' ability to reach glycemic goals.

Currently, patients with type 1 diabetes in the U.S. have limited therapeutic options. These include insulin and pramlintide, which was approved as an adjunct to insulin in 2006 and is not often used due to its complicated applicability and side

effect profile. In addition, there are no oral agents to improve glycemia in adults with type 1 diabetes. During the FDA EMDAC meeting on May 24th of this year, it was acknowledged that existing therapies for type 1 diabetes are inadequate and that more effective, convenient glucose management options are needed.

Achieving A1C levels with insulin alone is challenging due to the limitations of subcutaneous insulin replacement. Many patients experience excessive weight gain and peripheral insulin resistance, both of which are risk factors for hypertension and cardiovascular disease.

The burden of current treatment options has also been shown to adversely affect quality of life; therefore, there is a need for therapeutic options that improve glycemic control and reduce the risk of kidney disease progression and cardiovascular comorbidities in patients with type 1 diabetes and chronic kidney disease.

Next, I'd like to briefly discuss two important glycemic-related adverse event risks,

hypoglycemia and diabetic ketoacidosis. For patients with type 1 diabetes, our goal is to achieve optimal glycemia control and limit hypoglycemia and the incidence of diabetic ketoacidosis, both of which are acute, serious, and potentially life-threatening complications of type 1 diabetes and its treatment. Severe hypoglycemia is far more common than DKA. Both can be associated with severe health consequences, including hospitalization and mortality. Prevention of these conditions remains a cornerstone of care.

Effective management of type 1 diabetes requires proactive monitoring and timely interventions to prevent DKA. For DKA, patients need to be aware of the typical early warning signs, including blood glucose levels which may or may not be excessively elevated, the presence of ketones, and clinical situations such as a dislodged insulin infusion line or being very ill from any condition.

The standard of care put forth by the

American Diabetes Association, the JDRF, now called Breakthrough T1D, the EASD, and other national and international organizations is to treat DKA with fluids, rapid-acting insulin, and ingesting carbohydrates, along with glucose and ketone monitoring. The STICH protocol was developed by an international consensus group when SGLT inhibitors entered the market. The STICH protocol is merely an acronym of these standard recommendations. Specifically, patients would stop the SGLT inhibitor, inject short-acting insulin, consume carbohydrates, and hydrate with fluids.

At UCSD, we tell our patients that the symptoms of DKA are not just those of an elevated glucose value, but they include feeling nauseated with muscle aches and weakness, similar to having the flu. Having access to test their ketones is also stressed, but even if they do not have a ketone meter and suspect early ketoacidosis, I have them follow the STICH protocol until the issue has been resolved.

In summary, patients with type 1 diabetes

and chronic kidney disease are at an increased risk of glycemic and kidney complications. Despite advances in insulin therapy and glucose monitoring, most patients with type 1 diabetes and chronic kidney disease do not achieve glycemic control targets. We also recognize that long-term outcomes are influenced by the level of patient education and motivation to take control of their diabetes. Most use a continuous glucose monitoring device with alerts and alarms notifying the user of impending excessively high and dangerously low levels, many use an insulin pump, and there is guidance to help them measure ketone levels when indicated.

SGLT inhibition has proven to reduce heart failure, death from CVD, slow the progression of chronic kidney disease in people with and without type 2 diabetes. This is important, as the main risk factors and pathophysiologic findings of CKD and type 2 diabetes are similar in type 1 diabetes, supporting that the benefit should also apply to T1D. This highlights the urgent need for a new

adjunct therapy that will improve glycemic control and could help diminish the long-term complications from poorly controlled diabetes. Thank you very much, and I will now turn the presentation over to Dr. Davies.

Applicant Presentation - Michael Davies

DR. DAVIES: Good morning. My name is Mike Davies. I'm the Executive Director of Clinical Development at Lexicon. I will review the results demonstrating that sotagliflozin added to insulin therapy improves A1C and multiple other associated benefits in patients with type 1 diabetes and chronic kidney disease, a population at increased risk of morbidity and mortality linked to poor glycemic control.

First, let me walk you through the phase 3 clinical development program for sotagliflozin in patients with type 1 diabetes. Studies 309 and 310 were identical, 52-week, placebo-controlled trials. These studies enrolled adults with type 1 diabetes with an A1C of 7 to 11 percent. In these trials, insulin was to be optimized to prespecified fasting

and postprandial glucose targets during a 6-week run-in period prior to randomization. Optimization was continued throughout the 52-week period.

Patients were randomized to receive once-daily placebo, sotagliflozin 200 or 400 milligrams. The primary endpoint was assessed at week 24, after which patients can remain on assigned therapy in the 28-week safety extension period. At week 24 and beyond, investigators were unmasked to A1C and fasting plasma glucose values. This allowed investigators to use these measurements to adjust diabetes care. Given the similarities of these two studies and enrolled population, the data from Studies 309 and 310 were pooled for the present analyses.

Next, Study 312 was a 24-week, placebo-controlled trial designed to evaluate the efficacy and safety of sotagliflozin 400 milligrams compared to placebo when added to insulin. Unlike Studies 309 and 310, insulin optimization was not done prior to randomization but was used after randomization. Enrollment criteria was similar

across the three studies, including an eGFR greater than or equal to 45 milliliters per minute. Change in A1C at week 24 was the primary endpoint in the two identically designed phase 3 studies and a key secondary endpoint in Study 312.

In the intention-to-treat analyses, sotagliflozin demonstrated statistically significant benefits compared to placebo across the primary and predefined secondary A1C endpoint. The statistically significant efficacy demonstrated in the phase 3 studies and consistent findings across the prespecified subgroups allowed for evaluation of a subgroup that could gain even greater benefits like patients with type 1 diabetes and chronic kidney disease.

For the present post hoc analyses, the subgroup of patients with type 1 diabetes and chronic kidney disease was identified using the KDIGO guidelines. In our analyses, patients were considered to have CKD if they had a baseline eGFR of 45 to less than 60 milliliters per minute or an eGFR greater than or equal to 60 with an urine

albumin to creatinine ratio of 30 milligrams per grams or greater.

As a reminder, an eGFR of at least 45 was the entry criteria in the studies. This definition identifies patients who have a moderate to high risk of kidney disease progression and for whom KDIGO group recommends intervention be initiated to slow kidney function decline and reduce the risk of kidney failure. Across the T1D program, 458 patients, or approximately 15 percent, met this definition. Among this subset of patients, most patients met the definition with a UACR of 30 or greater, while approximately 30 percent of the subset had an eGFR of 45 to less than 60.

Within this T1D subgroup, baseline demographics and characteristics were generally balanced among the treatment groups and studies. Mean age was 45 to 48 years, and there was an even distribution of men and women. Most patients were white, and approximately half were enrolled in the U.S. or Canada. Most patients were considered overweight or obese based on body mass index.

Based on the T1D-CKD definition, mean eGFR was approximately 80 milliliters per minute with most having mild to moderate kidney impairment, and median UACR was approximately 60 milligrams per gram.

Baseline mean A1C ranged from 7.7 to 7.8 percent in the pooled studies and 8.3 to 8.7 in Study 312. This between-study difference and baseline is due to the 6-week insulin optimization period used in Studies 309 and 310. Overall, most patients had an A1C of less than 8 and a half percent. The average duration of diabetes was approximately 25 years, and roughly 40 percent of patients were receiving insulin via an insulin pump.

Now, turning to the results, both doses of sotagliflozin demonstrated significant and clinically meaningful reductions in A1C from baseline compared to placebo at 24 weeks. In the pooled studies from a baseline A1C of approximately 7.8 percent, the placebo-adjusted mean change in A1C at 24 weeks was 0.34 and 0.31 percent for the

200- and 400-milligram doses, respectively.

A similar benefit was achieved with sotagliflozin 400 milligrams in Study 312. From a baseline of approximately 8 and a half percent, the placebo-adjusted mean change was 0.45 percent. Importantly, these results and these two independent data sets were consistent with each other, and also with those observed in the ITT analyses.

While A1C is the gold standard for predicting microvascular complications, it does not capture how patients experience their diabetes control on a day-to-day basis. Time in range is a measure of day-to-day glycemic control and is defined as the percentage of time with a blood glucose between 70 and 180 milligrams per deciliter. Using results from a blinded continuous glucose monitor, or CGM, substudy, we evaluated time in range to better understand the glycemic benefits beyond A1C with sotagliflozin in the T1D-CKD subgroup.

At baseline, percent time in range, or the

green bars, was 50 to 59 percent across treatment groups; time above range in the yellow bars represents the time with blood glucose greater than 180 milligrams per deciliter; and the time below range in red bars represents the time with the blood glucose less than 70 milligrams per deciliter. At week 24, no appreciable change in the time in range was noted in the placebo group. A small change in time in range was observed in the 200-milligram group.

A larger improvement in time in range was found in the 400-milligram group. This increase translated into approximately four more hours in range per day. We acknowledge the limited sample size in the T1D-CKD subgroup, but these results are consistent with those observed in the 278 patients included in the pooled CGM substudy from Studies 309 and 310.

Next, we evaluated changes in body weight. In the pooled studies, significant reductions in body weight were achieved in both sotagliflozin doses compared to placebo at week 24. The

placebo-adjusted reductions in body weight with sotagliflozin ranged from 1.4 to 2.5 kilograms with the 200- and 400-milligram doses, respectively. Similar results were observed in Study 312 with a placebo-adjusted reduction in body weight of 2.8 kilograms with sotagliflozin 400 milligrams. This is important, as the majority of patients in the T1D-CKD subgroup were overweight or obese.

Next, we will review the safety results in the T1D-CKD subgroup. The safety profile is based on 274 patients treated with sotagliflozin. This includes 160 patients treated with sota in the pooled studies and 114 in Study 312. Mean exposure was approximately 11 months in the pooled studies and 5 months in Study 312. The overall safety profile of sotagliflozin in the T1D-CKD subgroup is largely similar to that in the overall T1D study population.

In all studies, the majority of patients in all treatment groups experienced an adverse event. In the T1D-CKD subgroup, the proportions of patients in each treatment group who experienced an

adverse event is comparable to that seen in the overall study population. Adverse events were mostly mild and moderate in severity. Overall, serious adverse events were similar in frequency between treatment groups. Sotagliflozin did not increase the adverse events leading to discontinuation through week 52. Three patients died during the clinical trials, one on sotagliflozin in Study 312 and two on placebo in the pooled studies.

In this table, we summarize adverse events typically associated with SGLT inhibitors that occurred at an incidence of at least 5 percent in any sotagliflozin arm. Across the studies, the most frequently reported adverse events with sotagliflozin were urinary tract infection, diarrhea, and increased ketones. In the pooled studies, sotagliflozin did not increase adverse events leading to discontinuation. No specific adverse event leading to discontinuation occurred in more than one sotagliflozin patient. In Study 312, we did observe a higher incidence of

adverse events leading to discontinuation, with DKA being the only event occurring in more than one patient.

Let's now review adverse events of hypoglycemia and DKA in more detail. Patients with type 1 diabetes frequently experience events of blood glucose less than 54 milligrams per deciliter or level 2 hypoglycemia. These types of events are associated with neuroglycopenia or symptomatic hypoglycemia. Across the trials, most patients experienced at least one event of a blood glucose less than or equal to 55 milligrams per deciliter. Moreover, many patients experienced more than one event, as demonstrated by the total number of events.

Importantly, treatment with sotagliflozin was associated with a lower number of events of blood glucose less than or equal to 55 milligrams per deciliter. When expressed as the number of events per patient per year, the event rate was lower with sotagliflozin relative to placebo within the T1D-CKD subgroup. A similar pattern was

observed in the overall T1D population.

Next, severe hypoglycemia, also referred to as level 3, was captioned as an adverse event of special interest. All suspected events of severe hypoglycemia were adjudicated by an independent committee. In the pooled studies, positively adjudicated severe hypoglycemia occurred more often with placebo compared to sotagliflozin. In Study 312, severe hypoglycemia was reported in 7 percent in the sotagliflozin group and 5 percent in the placebo group within the T1D-CKD population. Again, a similar pattern was observed in the overall T1D population for both study data sets.

Now, let's review DKA events. Similar to severe hypoglycemia, all investigative reported events of DKA and metabolic acidosis were adjudicated. This slide focuses on the positively adjudicated DKA events. Overall, the incidence of adjudicated DKA was increased with sotagliflozin compared to placebo in the T1D-CKD subgroup. In the pooled studies, 5 percent of patients receiving sotagliflozin 200 milligrams and 3 percent on

400 milligrams experienced a DKA event compared to 1 percent in the placebo group.

A similar imbalance was seen in Study 312 with 3 percent on sotagliflozin and 1 percent on placebo in this subgroup. All positively adjudicated events were considered serious. When adjusted for exposure, the incident rates of DKA was similar across groups in patients in the T1D subgroup and compared to the overall study population.

To conclude, the statistically significant primary and key secondary endpoints found in the phase 3 studies and consistent effects across multiple prespecified subgroups allowed for a selection of a T1D-CKD subgroup. Patients with type 1 diabetes and chronic kidney disease receiving sotagliflozin had significant improvements in A1C and body weight. These help manage risk factors in this population with a greater risk of disease progression.

The A1C and body weight results were replicated in two independent study cohorts. The

safety profile was consistent with that of the overall T1D population. There was no increased risk of severe hypoglycemia and a lower rate of level 2 hypoglycemia with sotagliflozin. An increased risk of DKA was found with sotagliflozin.

Collectively, these results support an improved benefit-risk profile in a subgroup of patients with type 1 diabetes and chronic kidney disease, a group at higher risk of disease progression. Thank you. I'll turn the presentation over to Dr. Granowitz.

Applicant Presentation - Craig Granowitz

DR. GRANOWITZ: Good morning. My name is Craig Granowitz. I'm Senior Vice President and Chief Medical Officer at Lexicon. I will present the efficacy and safety results in the GFR 60 to 90 subgroup. We want to acknowledge and make clear to the panel that this was not the specific CKD population we originally defined, as it was not part of the scientific consensus standard for CKD definitions that were utilized as our guide; however, this is a subgroup of patients with mild

to moderate CKD at elevated risk of complications and in whom sotagliflozin demonstrates an improved benefit-risk. Now, to the results.

The GFR 60 to 90 subgroup includes approximately 50 percent of the overall study population of more than 1300 patients across three separate trials, thus providing a substantial sample to evaluate the benefit-risk in this population. Presented here are the A1C reductions at 24 weeks in Studies 309 and 310 pooled and Study 312. Mean change for each treatment group is summarized in the table for each study group, and the difference in A1C compared with placebo is seen in the forest plot to the right.

Across all studies, the GFR 60 to 90 subgroup, highlighted in the color purple, achieved meaningful A1C reductions compared to placebo at 24 weeks. In studies 309 and 310, the greatest A1C reductions were achieved in this subgroup. Overall, A1C reductions were greater in Study 312, where an insulin optimization period was not included prior to enrollment, and patients had

significantly higher baseline A1C levels. While the point estimates in the pooled 309 and 310 studies, and the 312 study in the GFR less than 60 group, favored sotagliflozin treatment, the effects were less than the 60 to 90 group, and the confidence intervals cross unity.

Turning now to hypoglycemia, evidence from the clinical development program support a reduction in level 2 hypoglycemia with sotagliflozin in the overall population compared to placebo. As you can see in the table to the left, level 2 hypoglycemia was a common occurrence with approximately 15 to 18 events per patient per year or more than one per month.

The sotagliflozin-treated group experienced approximately a 20 percent reduction in events, which on average would correspond to approximately 2 to 3 fewer events per patient, per year. For severe hypoglycemia, the rates were similar to placebo and similar across all three GFR subgroups in the pooled 309 and 310 studies and the 312 study, with perhaps somewhat higher rates in the

GFR less than 60 group, although there were a very small number of events in this group. The overall rate of severe hypoglycemia was approximately 5 to 8 events per 100 patient-years.

Next, I'd like to focus on events of DKA. Sotagliflozin is associated with an increased rate of DKA, as was highlighted by Dr. Davies' presentation. The table to the left presents the incident rates per 100 patient-years for each treatment group from the phase 3 studies. The forest plot to the right shows the incident rate difference compared to placebo. The DKA rate was highest in the less than 60 group. The DKA rate in the 60 to 90 and greater than 90 groups were similar to the overall population in approximately 3 to 4 events per hundred patient-years compared to placebo.

In summary, the 60 to 90 subgroup provides an alternative and compelling benefit-risk option with clinically meaningful reductions in A1C, reduction in level 2 hypoglycemia, and a less pronounced increased risk of DKA in a group of

patients who remain at risk of cardiovascular disease progression. While this group of patients do not have the same level of renal impairment as the T1D-CKD subgroup, this group also excludes those with a GFR less than 60, where the A1C benefits may be attenuated and the DKA risk may be elevated.

Lexicon has developed an educational plan on the potential risks and appropriate use of sotagliflozin. This plan will inform patients and healthcare providers on the known risks associated with treatment to facilitate discussions, appropriate patient selection, and provide patients with step-by-step measures to maximize safety if they do expect or experience DKA.

Patient selection is the first step in minimizing the potential risks associated with sotagliflozin. As part of the educational program, Lexicon will ensure that healthcare providers and patients are aware of relevant patient characteristics that will help identify those who are most appropriate to receive sotagliflozin.

These include patients who are able and committed to maintain their prescribed insulin management program and are willing to self-monitor and follow sick day rules. We will also recommend against use of sotagliflozin in patients with a history of recurrent DKA in the past 12 months.

Education is important to ensuring the safe use of sotagliflozin; therefore, the educational plan will include specific materials for patients, caregivers, and the healthcare providers that will be distributed broadly across multiple communication channels. We look forward to working with the FDA and other organizations as we continue to collaboratively refine and implement these educational efforts.

While we are seeking a glycemic control indication for the T1D-CKD group for sotagliflozin, it was the results generated in a population of type 2 CKD patients that confirmed our strategy to target a T1D-CKD population. As such, I will present the result from SCORED, demonstrating long-term benefits of sotagliflozin in a population

of CKD patients with type 2 diabetes.

SCORED was a large, multinational, randomized, placebo-controlled study in a more advanced group of patients with CKD to evaluate the cardiorenal benefits of sotagliflozin. This study enrolled 10,584 adults with type 2 diabetes, chronic kidney disease, and additional cardiovascular risk factors. Screening A1C levels were greater or equal to 7 percent. The kidney-related criteria were a screening GFR of 25 to less than 60.

DR. FRIMPONG: Hello. I'm sorry. Joyce Frimpong, DFO. If you could just please give us a minute or two; we're having a little bit of audio-visual technical difficulties, and they're going to try and fix the issue. So we'll pause, everyone.

(Pause.)

DR. GRANOWITZ: Chair, where should I re-begin? I don't know when we lost contact. I'm happy to start right where I left off or at an earlier point.

DR. LOW WANG: If you can give us a second, we'll notify you which slide to go back.

DR. GRANOWITZ: Thank you.

(Pause.)

DR. LOW WANG: Okay. It looks like we're back online. If you could start with slide CO-55, that would be great.

DR. GRANOWITZ: Fifty-five. Thank you.

Lexicon has developed an educational plan on the potential risk and appropriate use of sotagliflozin. This plan will inform patients and healthcare providers on the known risks associated with treatment to facilitate discussions, appropriate patient selection, and provide patients with step-by-step measures to maximize safety if they do suspect or experience DKA.

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Patients were randomized to once-daily sotagliflozin 200 milligrams or matching placebo. Starting at week 4, study dose was to be uptitrated to sotagliflozin 400 milligram at the discretion of the investigator. The primary endpoint was a composite of total occurrence of cardiovascular death, hospitalization for heart failure, and urgent visit for heart failure.

During a median follow-up of 16 months, treatment with sotagliflozin reduced the risk of a

composite primary endpoint by 25 percent. As shown here, the curve separated early, with a sustained significant benefit observed at 3 months, and continued to diverge over the study period following randomization. The results demonstrated the benefits of sotagliflozin on long-term cardiovascular outcomes and supported the approval of sotagliflozin for reducing the risk of cardiovascular death and heart failure events in patients with type 2 diabetes at high cardiovascular risk.

A consistent benefit of sotagliflozin was seen across heart failure, atherosclerotic, and kidney-related outcomes. Of note, after the CV death endpoint, all remaining endpoints, except all-cause mortality, were nominally significant. The results in SCORED demonstrate the proven benefit of sotagliflozin in a group of patients with T2D enriched with more advanced kidney disease.

While we acknowledge that these results are achieved in a group of patients with type 2

diabetes and more advanced CKD and CV disease than the T1D-CKD cohort, the risk factors and pathophysiology of CV and kidney disease progression are similar in patients regardless of diabetes type.

The goal is to delay the progression of renal dysfunction for the identified T1D-CKD population to resemble the more advanced kidney and cardiovascular disease patients who were studied in SCORED. Thank you. I will now turn the presentation over to Dr. Pratley.

Applicant Presentation - Richard Pratley

DR. PRATLEY: Thank you, and good morning, everyone. My name is Rich Pratley. I serve as the Medical Director at the AdventHealth Diabetes Institute, and I'm a senior investigator and the diabetes program lead at the AdventHealth Translational Research Institute in Orlando, Florida.

My entire professional career has been dedicated to improving the management of patients with type 1 and type 2 diabetes, both in clinic and

through research. I've led numerous clinical trials, including those involving patients with type 1 diabetes and chronic kidney disease, and I was also an investigator on Studies 309 and 312 with sotagliflozin.

We now view cardiovascular disease and chronic kidney disease as a continuum that's underpinned by metabolic dysfunction, as illustrated by the progressive stages on this graphic. Although this perspective from the American Heart Association is focused on obesity and type 2 diabetes, patients with type 1 diabetes share a similar pathophysiology and risk for CKD, cardiovascular disease, and heart failure, and are equally well described by this continuum.

Indeed, 60 percent of adults with type 1 diabetes are overweight or obese, and by virtue of having diabetes, they can be classified as having stage 2. Without intervention, many of these patients will progress to stage 4, leaving them at high risk for cardiovascular events and death. Regardless of whether we're talking about type 1 or

type 2 diabetes, the underlying pathobiology is comparable. That's why the data from the SCORED study is so relevant to what we are discussing today. That means we already have evidence suggesting that sotagliflozin should have similar long-term benefits in patients with T1D and CKD.

Studies like SCORED have allowed us to provide evidence-based guidelines for managing CKM risk in T2D. The ADA and KDIGO groups have created detailed guidelines for the management of patients with diabetes. There are many treatment options to manage glucose, cardiovascular disease risk, and kidney disease for patients with T2D and CKD, including the SGLT2 class, which has been used extensively for the past 11 years. These agents are now approved for both cardiovascular and kidney indications for type 2 diabetes. These guidelines offer a multipronged approach that can be intensified based upon individual patient needs.

Unfortunately, at this point in time, there are few evidence-based recommendations for patients with T1D and CKD. Today's guidelines recommend

insulin to manage glucose in patients with type 1 diabetes and RAS inhibition for patients with CKD. As you can see, other than RAS blockade, the guidelines do not provide any specific recommendations to prevent cardiorenal-related events or heart failure in type 1 diabetes.

In the absence of specific therapies proven to decrease risk, it's even more important that we avoid the risks associated with poor glycemic control. Keeping patients in the target range becomes critical since these patients already have a heightened risk for cardiovascular mortality. That's why access to sotagliflozin is so important. It offers patients with T1D and CKD the ability to gain clinically meaningful reductions in A1C and improvements in time in range while not increasing the risk for severe hypoglycemia.

But also important are the benefits this therapy could provide in addition to glycemic control. Sotagliflozin was shown to decrease body weight by a clinically meaningful amount, and most importantly is the potential benefit of

sotagliflozin on long-term kidney and cardiovascular outcomes. While we do not yet have direct evidence of these benefits in patients with type 1 diabetes, the comparable pathophysiology in type 1 and type 2 diabetes supports the expectation that long-term benefits will be similar for patients with type 1 diabetes and CKD.

In my experience, treating patients with diabetes, I've realized that the careful selection of patients for treatment intensification is critically important regardless of the intervention. This is particularly true for mitigating glucose-related risks and when considering adjunct therapies. In general, patients with T1D and CKD have an established history that informs us about their level of engagement. Successful patients are good at monitoring their glycemic excursions, adjusting insulin, and managing their diabetes through using CGM and pumps. They're also knowledgeable about DKA and able to monitor ketones. These patients are often willing to take additional measures like

using sotagliflozin to improve glycemic control.

By the same token, though, we know that there are patients for whom sotagliflozin would not be appropriate, patients who are less engaged, who perhaps can't recognize the signs and symptoms of DKA, or who are unwilling to implement steps to mitigate it. In these patients, we often settle for less aggressive glycemic targets and treatment regimens; but again, patients with T1D-CKD have an established history that will inform our decision.

In patients who have CKD and have been managing their type 1 diabetes for many years, sotagliflozin offers a positive benefit-risk. These patients may choose to improve their glycemic control to limit hypo and hyperglycemic episodes that may add to the cumulative micro and macrovascular damage that they already have. Importantly, sotagliflozin does not increase the risk for severe hypoglycemia, but there is a risk for DKA. The risk is small but real, and it must be balanced against the expected benefits from improved glycemic control. Careful patient

selection and education can help mitigate the risk of DKA while allowing patients to benefit from sotagliflozin.

We urgently need a therapy with the potential to impact disease progression. Patients with T1D and CKD who are engaged in their disease and lifestyle management, and who are willing to initiate new treatments, should have access to sotagliflozin to improve their glycemic control, decrease their body weight, and help manage the risk for progression to DKD [sic] and other complications.

Thank you, and I'll now turn the presentation back over to Dr. Granowitz.

Applicant Presentation - Craig Granowitz

DR. GRANOWITZ: Thank you, Dr. Pratley.

The FDA has asked you to vote on the benefit-risk of our proposed T1D-CKD subgroup. It is a high-risk population where the benefit-risk assessment is different than the overall T1D population given the significant and serious health consequences they face beyond DKA alone. Our data

support that these patients have the greatest need for slowing disease progression and can benefit from sotagliflozin.

What we are targeting today is a high-risk subgroup of patients with T1D-CKD who have the greatest need for glycemic control. Both the T1D and CKD and the GFR 60 to 90 subgroups have significant unmet medical need and would benefit from near-term glycemic benefits and long-term potential for reduced CV risk and renal progression, but we acknowledge the GFR 60 to 90 subgroup removes the uncertainties in patients with a GFR of less than 60.

The first SGLT inhibitor was approved in 2013, and in the 11 years that have followed, this class of products has become well characterized and well known across a range of indications and uses. Sotagliflozin will fill an important unmet medical need as the first oral adjunct to insulin for T1D-CKD patients, and we look forward to your consideration and input on the favorable risk-benefit profile for this important subgroup of

patients. Thank you. We'd now be happy to answer your questions.

Clarifying Questions to Applicant

DR. LOW WANG: Thank you.

We will now take clarifying questions to Lexicon Pharmaceuticals. 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 of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

I'd like to open the floor to our advisory committee members, and please let me know if you have any clarifying questions for Lexicon Pharmaceuticals. First, I'd like to call on Dr. Konstam.

DR. KONSTAM: Yes. Thank you, and I appreciate the sponsor's presentation, which I

think was very clear and well done, and one overarching question. You appear to be seeking indication for type 1 diabetes and CKD, and it brought in the subgroup of patients with eGFR between 60 and 90. And I'm hearing that that is part of the population that you would like to see approved, but it doesn't seem that the FDA is asking us a question about that 60 to 90 subgroup. The question seemed to revolve around the earlier definition, which is an eGFR below 60 or greater than 60 with increased urine albumin and creatinine ratio.

Could you just clarify what exactly you're seeking?

DR. GRANOWITZ: Thank you for the question. The group that we're seeking -- if we could pull up CO-12, please -- is this group of patients with a GFR of 60 to 90 regardless of UACR.

If you could pull up slide 11, please? If you look in the group, based on the subgroup identified by the FDA, this excludes that group of patients with a GFR of 45 to 60, where you can see

in both the FDA briefing book and in our presentation today, there are greater uncertainties in that subgroup, both in terms of reduced A1C reductions and increased DKA risk. So the indication we're seeking -- if we could pull up 72, I believe -- is the 60 to 90 subgroup.

DR. YANOFF: FDA would like to provide further clarity on your question, Dr. Konstam.

DR. KONSTAM: Please.

DR. ARCHDEACON: We certainly invite the applicant to propose whatever group they want. The original group that they proposed was the 45 to 60, regardless of UACR greater than 60, with a UACR greater than 30, and that's fine if that is what they want to propose. Our voting question certainly asks about that population.

In addition, we then invite if you guys want to comment on any other population defined by eGFR and UACR. We are not necessarily suggesting anything. As we'll make clear in our presentations, our subgrouping was mostly intended to help us understand what the A1C reduction was in

various subgroups because glycosuria is related to GFR in this drug class. But we're inviting the committee to opine on any KDIGO subgroups where they think the benefit-risk is favorable without necessarily suggesting one.

DR. KONSTAM: Okay. Thank you very much. That's all for me at this point.

DR. LOW WANG: Thank you.

Cecilia Low Wang. I'd like to ask the next question, and then we'll move on to the other committee members. How do you feel that the results from SCORED can be applied to the 60 to 90 group that you described in the TANDEM trials?

DR. GRANOWITZ: If we could pull up slide CO-22, both of these groups have elevated risk, the group that we propose -- and I'm sorry; it will take me one moment to get to the question. I just wanted to frame it that both these groups have an elevation in cardiovascular and renal risk. The goal is really to prevent the progression of the patients to the SCORED group.

What we've identified is that these are

potential benefits to prevent patients from having that level of advanced renal disease. So the goal on the glycemic indication is to have the short-term benefits on glycemic, and those are certainly related to the progression of the renal disease, to those group of patients that have more advanced renal disease where the non-glycemic events and the rapidity of progression to end-stage cardiovascular and renal disease are more apparent.

DR. LOW WANG: Cecilia Low Wang. I think what I'm understanding that you're saying is that the SCORED results don't directly apply to the population, but you're hoping to prevent people from being able to be eligible for SCORED.

DR. GRANOWITZ: Exactly. Right, there are potential benefits for a group of patients by seeking a glycemic indication and not an outcome indication, preventing the patients from being at such high risk of developing that disease state.

DR. LOW WANG: Thank you. I understand.

I'd like to next call on Mr. Tibbits.

MR. TIBBITS: Thank you. I think my

question is for Dr. Granowitz.

DR. LOW WANG: Please go ahead and state your name.

MR. TIBBITS: Oh, sorry. Paul Tibbits. Thank you for your presentation to all of you, and I appreciate the openness of thinking about other groups beyond the original group that you were discussing.

I'm looking at, I think, a combination of slides, 50 and 53, and specifically thinking about the different dosage that was given to populations. And it seems like the smaller dose had a reduced but still significant impact on A1C but also had less of a risk of, let's say, DKA compared to 400.

I'm thinking about progressing a patient from 200 to 400. What have you found through the trial? Is there any ability to predict which patients may be at increased risk of DKA if they were to progress from 200 to 400 if the physician thinks that the glycemic control is not exhibited enough with the smaller dose?

Thank you. That's my question.

DR. GRANOWITZ: We really wanted to provide, with the two doses, the options, based on the risk-benefit. And as we showed in the presentation, particularly beyond A1C, there were other benefits, particularly weight reduction and time in range, which Dr. Davies showed -- and I can certainly pull those slides up for this subgroup, if you'd like -- balanced against the DKA.

It is hard to make judgments between the 200 and 400 regarding the DKA risk specifically because the confidence intervals are fairly wide and the number of events are quite small, as you can see in this slide. So we really wanted to provide the option for healthcare providers to have that ability to increase the dose if they, in conjunction with the patient, determined that they wanted some of those other potential benefits, like time in range, weight loss, blood pressure.

DR. LOW WANG: Alright. Let's move on to Dr. Wang.

DR. WANG: Thanks. Thomas Wang. I also want to thank the sponsor for the nice

presentation. I have two questions, but if time is short, I can just start with my first, and it's going back to the use of the SCORED trial and relating the findings from the SCORED trial to the current panel review.

I appreciate that the pathophysiology of complications of diabetes overlap between type 1 and type 2, but I imagine that there are other differences in the study population in the SCORED trial versus the TANDEM trials, or the phase 3 trials, for type 1. The one that jumps out to me is age. There's about a two-decade difference in age. In the type 1 diabetes trials, it looked like the age was in the mid 40s, and in the SCORED trial, the median age was 69.

I wonder if the sponsor could comment on that and any other differences. For instance, is there a baseline table of the two sets of trials that you might be able to show later side by side?

DR. GRANOWITZ: Yes. I'll pull up the slide, and perhaps, Dr. Davies, you might want to comment on some of the baseline demographics, and

I'll pull that slide up for you, Dr. Davies. Oh, it's a red dot. Okay. I apologize.

Can you see those, Dr. Davies?

DR. DAVIES: I can see. Mike Davies. Yes, I acknowledge that the SCORED population is about two decades older -- they are older -- but the type 1 population has had their disease for over 25 years, and disease duration is really a modifier. So they're likely to experience their outcomes earlier because of the longer duration of the disease.

Also, 60-65 percent are overweight or obese, so they have the risk factors, and these studies in the inTandem trials were designed to be glycemic-controlled trials and not cardiovascular risk, so they weren't enriched for those other factors.

DR. GRANOWITZ: Perhaps Dr. Vaduganathan can also --

DR. LOW WANG: Actually, just a quick question.

Dr. Wang, do you have a follow-up question

for the applicant?

DR. WANG: No, on that first question, I'm ok with that response.

DR. LOW WANG: Okay. Terrific.

I'd like to call on Dr. Irony.

DR. IRONY: Thank you. Ilan Irony. My question is, I think, for Dr. Pratley, the investigator in this trial. In terms of instructions on eligibility and monitoring for the STICH protocol, how often were the patients followed in the trial? There are two trials that you participated, 312 and 319, I think, in terms of the compliance with the STICH protocol.

DR. PRATLEY: Rich Pratley. Yes, I was an investigator in 309 and 312, and at that time, we were already aware of the risk of DKA with SGLT2 inhibitors. So the investigators were educated about how to talk to patients about DKA. The patients themselves had information about DKA and risk mitigation, including guidance. It was very much like the STICH protocol. They had access to the investigative sites if they became ill, and

they were provided with finger-stick ketone monitoring devices during the trial, and they were encouraged to monitor regularly. If we saw increases in ketones, that raised red flags.

We talked to the patients about any symptoms that they might have, so we followed them pretty closely in the trial. But I'd emphasize that there is a difference between patients who participate in trials and our clinic patients. Oftentimes, the patients that participate in trials are not our own patients that we have been treating for years and have that sense of their engagement. So there are some subtle differences between this patient population and our clinic populations who I know very well.

Did that answer your question?

DR. IRONY: Yes. Thank you, Dr. Pratley.

DR. LOW WANG: Thank you.

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

DR. EVERETT: Thank you. Brendan Everett. I had a similar question to Dr. Wang. I just want to push the sponsor a little bit on this. I've

made a table here by hand, which I'm happy to share with you, but I'd love it, if you don't have the data, if you could maybe prepare it during the break, where we look at a number of risk factors, really, to address this question of how comparable the populations enrolled in the type 1 diabetes, the three trials, are with SCORED.

I also noted the difference in age, but the other risk factors that would come to mind for me, with respect to progression of kidney disease, which appear to be different, are A1C baseline eGFR, body mass index, and I was wondering a couple other things, which I couldn't find in your presentation, including the proportion of male and female patients, UACR at baseline, blood pressure, and the use of ACE inhibitor and ARBs.

So since we're trying to extrapolate data from one population to another, I think there may nephrologists in the audience here who may know better than I of risk factors for the progression of kidney disease, and I think we'd like to be able to see those in a tabular format with the three

series trials, 309, 310, 312, and SCORED, next to one another to see if we think that the reference populations are comparable, at least at baseline.

DR. GRANOWITZ: Yes. Thank you. We have some of those prepared now. I think we might be able to answer some, and I think there's a more comprehensive list we could provide after the break.

Dr. Davies, do you want to comment specifically on some of the factors? And then if there's a clinical context question, perhaps we could have Dr. Vaduganathan answer.

DR. EVERETT: I think we just want a table up on the slide set, really is the question.

DR. GRANOWITZ: Okay. Then perhaps we'll wait till after the break, then we can give you a comprehensive list of what we have, and we can take your list and make sure we have what you you're looking for.

DR. EVERETT: Thank you.

DR. LOW WANG: Okay. Terrific. So we'll take a look at that when we have some time later.

Dr. Newman?

DR. NEWMAN: Thank you. Connie Newman. Could you please show slide CO-53? The title says that there's an increased risk of diabetic ketoacidosis lowest among the eGFR subgroup of 60 to less than 90. Can you please explain why you say that in the title? It seems to me that each group has an increased risk of diabetic ketoacidosis.

DR. GRANOWITZ: Yes. They all have an increased risk. I think what we are trying to refer to in the title of that slide is if you look at the 60 to 90 subgroup -- again, all those groups are to the right of unity, so we acknowledge that they all have an increased risk of DKA, but perhaps that group has the smallest increase compared to placebo.

Again, it's very small numbers, point estimates, but again, I think we all acknowledge, and I think the most important takeaway from that slide is the less than 60 group clearly appears worse with very wide confidence intervals, but the

point estimates are farther to the right than the 60 to 90 or greater than 90 group.

DR. NEWMAN: Thank you. It seems to me that what you said is correct, that each group has an increased risk of diabetic ketoacidosis that does not diminish with reduced GFR.

DR. LOW WANG: Cecilia Low Wang. So just staying with the DKA risk question, was there a standard protocol for DKA prevention during the clinical trials, 309, 310, and 312?

DR. GRANOWITZ: Yes. Dr. Pratley, do you want to comment on the study conduct as an investigator?

DR. PRATLEY: Rich Pratley. Sure. Yes, there were standardized guidelines in all three studies, 309, 310, and 3:12, which included baseline finger-stick ketone monitoring and followed largely the STICH guidelines. So if people developed any symptoms, they were to stop the SGLT2 inhibitor, contact the site immediately, and additional information was then given to the patients about dosing with insulin, carbohydrates,

and so on and so forth. If patients became acutely ill and weren't able to manage as outpatients, they were then referred to emergency rooms.

DR. LOW WANG: Thank you. I'm Cecilia Low Wang. Could you please show slide 46? I think what I'm seeing here is that the relative DKA risk seems to be attenuated in the type 1 diabetes and CKD subgroup relative to placebo group, but the overall risk is actually increased compared to the overall type 1 diabetes safety population, is what I see here, and this is despite that standard protocol for DKA prevention.

So I think I'd like to move on now to Dr. Drake.

DR. DRAKE: Thank you. I think a lot of this discussion today will focus around diabetic ketoacidosis, but I think it was also important to recognize hypoglycemia, which you acknowledged early has a very, very significant impact on these patients, and in fact is lessened in this study, so that's very nice to see.

That said, I just have a couple questions

here. Was there any way of identifying which patients were -- and we know that hypoglycemia can have very severe outcomes for patients. Was there any way of identifying which patients were more likely to develop those, for instance, hypoglycemia, those on continuous pumps or, for instance, those on subcutaneous? Was there any differential between that or those who used a continuous glucose monitor versus those who didn't, who had severe hypoglycemia episodes?

DR. GRANOWITZ: Dr. Davies, I know we've looked at the criteria related to DKA. Do you have information you can add on severe hypo?

DR. DAVIES: Mike Davies. We did all the analyses around the DKA trying to identify risk factors. Since we acknowledge that there's no real increase in severe hypo, we didn't really interrogate that too much.

DR. DRAKE: Okay. Thank you. Matthew Drake.

DR. LOW WANG: Next, Dr. Parsa.

DR. PARSA: Afshin Parsa. I'm still

thinking about the DKA and, obviously, we can have mild, moderate, or severe DKA that can either be managed at home or sent to the ER hospital. So given that the big counterweight here, apart from the benefits, are the risks of DKA, do you have any data on the severity of DKA, how many people required hospitalization, and what categories they fell in?

DR. GRANOWITZ: If we could pull up the slide that looked at the adjudicated and unadjudicated DKA, I can comment first on the investigator-reported versus positively-adjudicated DKA, and all of these DKA events were hospitalized, to my knowledge. All these patients were ultimately admitted to the hospital, and there were a larger percentage of investigator identified than ultimately adjudicated, as is often and usually the case because they have more information to the adjudication committee, and most of those are related to levels of acidosis that are predefined.

But you can see that the ratios between the investigator reported to the positively

adjudicated, if you look at, for example, the three columns on the left, the rate between the investigator reported versus the positively adjudicated are similar across the group. So they're, again, always greater with drug treatment, but there's no bias towards the drug treatment in terms of a reduced rate for the ultimately positively adjudicated.

If we want to look at the underlying causes, we have that slide, the underlying cause of the DKA. Most all the cases had an identified underlying cause associated with the development of the DKA, and largely those were related to changes in health status, whether it was infection, or illness, or an insulin issue. None of those seem to be necessarily related to the severity of the DKA event when they occurred.

DR. PARSA: So then all of these were hospitalized, all these.

DR. GRANOWITZ: Yes.

Dr. Pierce [sic], that's correct; all hospitalized, yes.

DR. LOW WANG: Dr. Everett?

DR. EVERETT: Just a quick clarifying question on that last slide. One group of events was blue and the other was purple, but I wasn't sure what the distinction was between the two.

DR. GRANOWITZ: Oh, I'm sorry. We were carrying our color coding forward, and the title of the slide has the name in it. I'm sorry I didn't draw your attention to it. The one in blue is the T1D-CKD group and the right is the --

DR. EVERETT: So if you go back to the prior slide just with that.

(Brief pause.)

DR. EVERETT: Perfect. Thank you. I just didn't understand --

DR. GRANOWITZ: I apologize for that. I should have been clearer.

DR. LOW WANG: Next, Dr. Roy-Chaudhury, and just a quick reminder to speak closer to the microphone.

DR. ROY-CHAUDHURY: Great. Thanks very much.

DR. LOW WANG: And go ahead and please state your name.

DR. ROY-CHAUDHURY: Prabir Roy-Chaudhury. So two questions, and the first is probably more of a philosophical sort of question. Looking at your pathway from the previous application in 2019, the goal seems to have been to change the risk-benefit profile, so identify a group of patients where you'd have a greater benefit, ideally a greater risk but even a greater benefit with same risk would be useful.

When you've gone from the initial group that you were interested in, so the 45 to 60 with UACR greater than 30, plus the 60 to 90, from just 60 to 90, you've reduced the risk, but looking at your own slides that you showed earlier, you've potentially reduced the benefit as well. Do you want to comment on where that leaves us, potentially, with the whole risk-benefit ratio?

DR. GRANOWITZ: Yes, I'll provide my comment from the company, and then perhaps Dr. Cherney can comment from a nephrologist perspective because I

think a lot of these we're talking about are renal.

If we could pull up slide CO-22, this slide, I'm bringing up, if you look at the bottom three rows of GFR, and that's stage 2, stage 3, and stage 4 -- and again, this is a retrospective look, but it's a 10-year look of patients with dysfunction going to heart failure events, so really using that as representative -- you can see all of the groups are to the right of unity, and that's again compared to those with a GFR greater than 90.

If you look at the middle two GFR groups, the top and the middle group, they are roughly representative of what we're calling the GFR 60 to 90 in the first row, and then the group of T1D-CKD in the second row. And you can see that the risk of progression in the T1D-CKD group by this analysis is 2- to 3-fold, 2.6-fold greater than those with normal GFR, and the group 60 to 90 has about a 34 percent increased risk compared to the overall group.

So we try to find a group -- and these two

groups are really balancing the short-term, benefit-risk of the glycemic management versus the long-term potential for these patients to progress to end-stage disease.

DR. ROY-CHAUDHURY: But you're moving from the group that could have had some of the 267 percent increase to the group that just has the 34 percent increase.

DR. GRANOWITZ: Yes. Maybe I'll let Dr. Cherney comment on that as well.

DR. CHERNEY: David Cherney. So there's absolutely a spectrum of disease here. The patients who are at the CKD stage 2 level of 60 to 90, whereby there seems to be the greatest certainty around glycemic lowering as well as the other effects that we saw from a metabolic perspective, those benefits are seen in those patients with bigger confidence. And they also still have that higher risk of developing cardiorenal complications over time, recognizing that this is a spectrum of disease, including people with simple impairment and kidney function,

which is augmented and accelerated in those patients with GFR, even in the stage 2 range with albuminuria.

So that's where there is that augmented potential for benefit; and also thereby to prevent them from declining further with sotagliflozin down into the range where there is even greater risk like in the SCORED trial as we were describing before. Thank you.

DR. ROY-CHAUDHURY: My second question was at the other end of the spectrum, which was very much about data. I think building upon what Dr. Everett said, do you have any data which describes the impact on UACR and eGFR in two additional groups? So one would be the type 1 diabetes subset, and then the second would be -- and I quite liked what you did with the matched SCORED data, so SCORED was obviously in moderate to severe CKD. But in the original group that you had identified, which was mild to moderate, do you have any data on UACR changes and eGFR changes?

DR. GRANOWITZ: Yes, I'll pull that up, and I'll start first with the UACR. And again, at some point, perhaps Dr. Cherney can comment on this as well. But what you see, again, is the subgroup of patients that was the T1D-CKD that had albuminuria because, obviously, we're not going to be able to show a reduction in albuminuria where they don't have the albuminuria. And what you see in this study is that there is a reduction in the UACR with treatment in that group of patients out of the T1D-CKD cohort.

David, you might want to comment, and I'll keep you up here for the GFR because that's a bit more complicated.

DR. CHERNEY: David Cherney. The effects on albuminuria and other markers of physiological benefits with SGLT inhibitors are very consistent with what we see here. Typically, these therapies induce approximately a 30 percent or more reduction in albuminuria across different cohorts of patients, including those with type 2 diabetes, non-diabetic CKD; and we see an analogous kind of

effect with SGLT inhibitors in this panel and also with other members of the class. So this is a very consistent effect that we see.

From a GFR perspective, this is a group of patients where we see the same initial dip in GFR, which is thought to reflect the beneficial hemodynamic effects of the SGLT inhibitors, which reflects a reduction in glomerular pressure, which we can see on the left-hand side of this graph. This dipping in GFR is thought to reflect decreased glomerular hypertension and is linked with the reduction in albuminuria; and over time, what we see is a stabilization effect whereby GFR dips and then returns back toward baseline.

If this was an enriched cohort with lots more albuminuria, we would typically expect to see the gray placebo group decline much more quickly and then cross the lines of the blue sotagliflozin-treated patients at around 12 to 18 months. This is, of course, a lower risk group of patients that tends to decline more slowly, so we don't see that crossing. But this is an

analogous pattern that we see in, essentially, every slide with SGLT inhibitors, including patients with type 1 diabetes.

I just want to comment that many of the other physiological benefits that we see across SGLT inhibitor is around hemoconcentration, around effects on uric acid, which are linked with physiological benefits. Those are also consistent in people with type 2 and type 1 diabetes, suggesting analogous effects. Thank you.

DR. GRANOWITZ: Dr. Cherney, if you want --

DR. LOW WANG: Actually, our time is getting very short, so I'd like to move on to the next person.

Dr. Seliger?

DR. SELIGER: Thank you. Steve Seliger, and thanks, everyone, for the wonderful presentation, and maybe as a follow-up a bit to Dr. Roy-Chaudhury's question. I might have missed this, but among the subgroup that you're suggesting eGFR 60 to 89, what proportion had at least A2 albuminuria? And I think this gets to the question

of who is really at risk for kidney disease progression. And conceptually and clinically, when we look at the KDIGO guidelines and the heatmap, which is shown in one of the slides here, the group with GFR 60 to 89 and A1 or normal albuminuria are not considered at great risk.

Do you have a sense of how many might have been in that with A2 of more?

DR. GRANOWITZ: Yes. Dr. Davies, do you want to comment?

DR. DAVIES: Mike Davies. Yes. Roughly, in in the people who had an UACR above 30, about 75 percent were in the A2 range or the 30 to 300.

DR. SELIGER: I guess my question is more, among those with a GFR of 60 to 89, what proportion had that A2 albuminuria? Is it 10 percent, 30 percent?

DR. DAVIES: 60 to 90?

DR. SELIGER: Among the eGFR 60 to 90.

DR. DAVIES: Oh, okay. I would have to get you that.

DR. GRANOWITZ: I can answer not exactly,

but very close --

DR. SELIGER: Sure.

DR. GRANOWITZ: -- is that if you look, the T1D-CKD group was about 70 patients that had that versus 250 in the overall group. The only difference is that the 60 to 90 doesn't have those greater than 90 that might have had albuminuria, but I think it's quite small. I would guess it's about 80 percent in the 60 to 90 group that did not have albuminuria.

DR. SELIGER: Thank you.

DR. LOW WANG: Thank you.

Dr. Onumah?

DR. ONUMAH: Barbara Onumah. Just a quick question about the persons who had DKA during the study, I was wondering if there were any peculiar characteristics about those persons after they were adjudicated to figure out if there was something about them that put them at risk for DKA. And just a follow-up question for that, in the numbers for the persons who had DKA, were there repeat DKAs? So did they have a second DKA after that?

DR. GRANOWITZ: Yes. Thank you for that question. And again, perhaps I'll comment, and if Dr. Pratley has a different point of view, you can quickly comment because I know we're very short of time. But it seems that if you look at those that are on the SGLT inhibitor, it is seen as really another potential risk factor, but the trigger factors -- the infections, and illness, and insulin -- seem to be roughly the same, and the course of the DKA event seems to be roughly the same.

There was one patient that had two adjudicated DKA events. The first didn't have an underlying precipitating factor that was identified, and that patient was restarted on therapy. They had a second event that was attributed by the adjudication committee to concurrent alcohol use, and after that, the patient was stopped.

DR. ONUMAH: Thank you.

DR. LOW WANG: So I'd like to delay the break just a little bit. I think there are two

more panel members who have questions, so brief questions, brief responses.

Dr. Konstam?

DR. KONSTAM: Yes. Thanks. I share some of my colleagues concerns about the applicability of the SCORED data to a type 1 population, in general, and the specific population you're asking for the indication in. But I'm trying to figure out how to do that, or how I can estimate going from what we know about your drug in type 1 diabetes, to knowing what the magnitude of the cardiovascular benefit is going to be.

I want to point out, you said a couple of times that the pathophysiology of the large vessel cardiovascular disease was the same in type 1 diabetes and type 2 diabetes. I don't know that at all because, in fact, in type 2 diabetes, there's no association, there's no correlation, between glycemic control and large vessel atherosclerotic disease. There clearly is with regard to microvascular disease; and there, I think it's more linked to the metabolic syndrome, in general, and I

think those are the elements that SGLT2 antagonists are specifically targeting.

So that's not present here, so my question boils down to, when we're trying to figure out risks-benefits, or say what exactly can we expect as the benefit, how do we go from the degree of glycemic control to jumping to say, ok, now here is the cardiovascular benefit? How do we do that?

DR. GRANOWITZ: Yes. Thank you for the question. I'll ask Dr. Vaduganathan to address that, please.

DR. VADUGANATHAN: Thank you. Muthia Vaduganathan. I fully agree that the pathophysiology of clinical events in type 1 and type 2 diabetes is perhaps distinct. Often, the onset of cardiovascular events occurs much, much earlier in type 1 diabetes and is more strongly linked with abnormal glycemic control; and that's been shown that A1C, even as a predictor of heart failure, major adverse cardiovascular events and cardiovascular death has a much steeper incline in terms of increments of risk than compared with

comparable populations of type 2 diabetes.

Furthermore, the effects on intermediate markers with sotagliflozin in type 1 and type 2 diabetes of cardiorenal risk, for instance blood pressure, A1C, albuminuria reduction, is highly comparable in these populations, so the anticipated benefits would appear to be similar.

Of course, this is an extrapolation. Many of these patients were well represented in the adjacent SOLOIST worsening heart failure trial, which was the dedicated heart failure outcomes trial with sotagliflozin. That better represented older patients and younger patients, as well as patients with eGFRs of 60 to 90, which, of course, SCORED did not include.

DR. KONSTAM: Yes. I'll just say that maybe in the afternoon, folks can come up with some data to demonstrate this, but I'm not aware of any data that allows you to extrapolate from glycemic control to the rate of MIs, strokes, et cetera. And maybe if you have data like that, we could see that because then at least we could say, ok -- hold

on a second. Glycemic control, we know that elevated A1C is associated with cardiovascular disease, but that doesn't seem to be the straightforward mechanism of the benefit of the drugs because before SGLT2 antagonists came along, there was no hypoglycemic agent that had demonstrated a reduction in major cardiovascular events; so anyway, whatever you want say.

DR. LOW WANG: Okay. Thank you.

Right now, we'll take a quick 10-minute break.

Panel members, please remember that there's no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We'll resume at 10:45.

(Whereupon, at 10:34 a.m., a recess was taken, and meeting resumed at 10:45 a.m.)

DR. LOW WANG: Welcome back. We will now proceed with FDA's presentations, starting with Dr. Mari Suzuki.

FDA Presentation - Mari Suzuki

DR. SUZUKI: Good morning. My name is Mari

Suzuki. I'm a clinical reviewer in the Division of Diabetes, Lipid Disorders, and Obesity. This is an outline for what we will cover today. I will be presenting an overview of the sources of clinical data submitted in support of the revised glycemic control indication, then I will describe the different approaches used by the applicant and by the FDA to reanalyze the efficacy and safety data.

Dr. Wenda Tu will present FDA's reanalysis of the primary and secondary efficacy endpoints from the TANDEM program. I will then present the key findings of the clinical safety review of the resubmission focusing on hypoglycemia and diabetic ketoacidosis in patients with type 1 diabetes and chronic kidney disease.

Lastly, Dr. Justin Penzenstadler will then discuss considerations related to potential non-glycemic benefits observed in cardiorenal outcome trials conducted in patients with type 2 diabetes and other comorbidities. We will close our presentation today with an integrated benefit-risk assessment.

The TANDEM program included three studies conducted in patients with type 1 diabetes. First, I am displaying a schematic of Study 309 and 310. These were identical trials conducted in the United States and Europe, respectively. Study 309 and 310 featured adults with type 1 diabetes inadequately controlled with insulin, either by multiple daily injections or continuous subcutaneous insulin infusions. Participants must have a diagnosis of type 1 diabetes for at least one year with an A1C 7 to 11 percent and an eGFR greater than or equal to 45.

These studies were multicenter and randomized subjects to double-blinded treatment with sotagliflozin 200 milligrams, sotagliflozin 400 milligrams, and placebo. Following a 2-week screening period, there was a 6-week insulin optimization period and a 2-week run-in period for placebo tablet adherence. Patients with greater than 80 percent adherence were then randomized to one of three treatment groups, sotagliflozin 200 milligrams, sotagliflozin 400 milligrams, or

placebo.

The core treatment period was 24 weeks with a 28-week double-blind extension period. The primary endpoint was assessed at week 24 and was changed in baseline and A1C. With the first sotagliflozin dose only, patients were instructed to reduce their mealtime bolus insulin dose by 30 percent with subsequent adjustments to be made by the investigator.

Study 312 was the third pivotal study which randomized only to double-blinded placebo or sotagliflozin 400 milligrams. The eligibility criteria were similar to Studies 309 and 310. In contrast to those studies, there was no insulin optimization period. All patients participated in a 2-week screening period with a subsequent run-in period for placebo tablet adherence. Eligible patients were randomized to either sotagliflozin 400 milligrams or placebo treatment for a 24-week treatment period. The primary endpoint was assessed at week 24 and was a composite of the proportion of patients with A1C less than

7 percent, no episode of severe hypoglycemia, and no episode of diabetic ketoacidosis.

Most participants enrolled in the TANDEM program had preserved eGFR and no evidence of albuminuria, and thus did not meet the applicant's definition of CKD. The table here classifies TANDEM program participants by Kidney Disease: Improving Global Outcomes, or KDIGO, categories for prognosis of CKD by eGFR and albuminuria. The columns going left to right represent increasing urine albumin creatinine ratio, or UACR, and the rows going top to bottom are worsening eGFR subgroups.

About 10 percent of TANDEM program participants had evidence of microalbuminuria and another 3 percent had evidence of macroalbuminuria. Less than 5 percent had an eGFR below 60. Given the limited clinical data available, there are inherent challenges to calculating accurate estimates of treatment effect of sotagliflozin on A1C across the applicant's revised target population.

The applicant and the FDA relied on two different approaches to addressing those challenges. To estimate the treatment effect, despite the limited data available, the applicant grouped all the participants who met the criteria for their revised target population together. This includes all subjects with an eGFR 45 to less than 60 or subjects with an eGFR greater than or equal to 60 and UACR greater than or equal to 30. There are disadvantages to this approach given that the A1C lowering effect of sotagliflozin is mediated by glucosuria.

First, it assumes that subjects with eGFRs ranging from 45 to over 100 will experience similar reductions in A1C despite the correlation between glucosuria and eGFR. In addition, study participants with eGFRs below 60 -- that is, the individuals likely to experience the smallest A1C reduction -- contribute the least amount of the data to the reanalysis of efficacy. Thus, the approach may overestimate the treatment effect that would be experienced by patients with eGFRs below

60.

Finally, this approach discards 84 percent of the data from TANDEM that came from patients with type 1 diabetes without CKD. Discarding these data avoids any uncertainty about the relevance of data from patients without albuminuria to patients with albuminuria; however, because the magnitude of glucosuria is known to depend on eGFR but not on UACR, the data from TANDEM participants without albuminuria might be informative to the A1C lowering effect of sotagliflozin in patients with type 1 diabetes and CKD. For example, data from participants with an eGFR of 75 and a UACR less than 30 could help inform the estimate of the treatment effect in patients with an eGFR of 75 and a UACR greater than 30.

FDA defined different subgroups in the TANDEM studies than the applicant. The FDA approach provides a complementary perspective to the applicant's approach to the reanalysis of TANDEM. The FDA approach was selected because it provides estimates of A1C reduction across the

range of kidney function included in the applicant's revised target population and because it makes use of all data collected in TANDEM.

The FDA approach is intended to provide estimates of A1C reduction to help inform overall benefit-risk assessments for any proposed population, including the applicant's proposed T1D-CKD population. FDA also used the same approach to assess other endpoints, as the pharmacodynamic effect of sotagliflozin may also be relevant for safety.

The FDA approach to the evaluation of efficacy and safety for the revised target population attempts to address the relationship between glucosuria and eGFR. FDA calculated treatment effects according to eGFR subgroups corresponding to CKD stage 1, marked by the blue box; CKD stage 2, marked by the green box; and CKD stage 3a, marked by the yellow box, regardless of UACR.

This approach allows the use of all data from TANDEM participants who belong to each eGFR

subgroup. It does assume that UACR and glucosuria are not related and that findings of efficacy in subjects without albuminuria can be generalized to otherwise similar patients with albuminuria. To be clear, the FDA subgroups are only intended to provide estimates of A1C lowering effect across the range of eGFRs included in the applicant's revised target population. The estimates are intended to inform benefit-risk assessments, and in any proposed population, including the applicant's revised T1D-CKD population. Ultimately, both the applicant's approach and FDA's approach are post hoc analyses, and both approaches have disadvantages.

The applicant proposed that the SCORED study provides additional efficacy data for glycemic control. SCORED is a cardiorenal outcomes trial conducted in patients with type 2 diabetes, moderate to severe chronic kidney disease, and other cardiovascular risk factors.

The study design was an event-driven cardiorenal outcomes trial with randomization to

double-blinded sotagliflozin or placebo. Sotagliflozin dose was initiated at 200 milligrams and uptitrated to 400 milligrams as tolerated after at least 4 weeks. Patients were followed for a median of 16 months. The primary endpoint was a composite of hospitalization for heart failure, cardiovascular death, an urgent visit for heart failure. We will discuss this endpoint later in our presentations.

The magnitude or durability of the effect on glycemic control is difficult to extrapolate to a population of obligate insulin users who titrate insulin regimens to individual glycemic goals. For these reasons, we will not present the glycemic data from SCORED.

I will now turn the presentation over to Dr. Wenda Tu to present FDA's assessment of the efficacy data from TANDEM for the revised indication for sotagliflozin of improved glycemic control in patients with type 1 diabetes and CKD.

FDA Presentation - Wenda Tu

DR. TU: Good morning, everyone. My name is

Wenda Tu. I'm the statistical reviewer of this application. I'll be presenting the efficacy results of the TANDEM studies by eGFR subgroup. Here's an outline for my presentation. First, I'll provide a brief summary of the study designs for the TANDEM program. An overview of the subgroup analyses will be followed by the details of the statistical methods applied to the subgroup analyses. My presentation will end with a description of the analysis results and a summary of the overall evidence provided by the efficacy analysis.

The TANDEM program consisted of three studies. Studies 309 and 310 share the same study design, and therefore were pooled for efficacy and safety analysis. Both studies were phase 3, multicenter, randomized, double-blind, placebo-controlled and parallel group studies. Each study consisted of a 2-week screening period; a 4-week insulin optimization period; a 24-week core treatment period; a 28-week, double-blind, extension treatment period; and a follow-up period.

Each study had three treatment arms: the sotagliflozin 200-milligram arm, the sotagliflozin 400-milligram arm, and the placebo arm. The pooled sample size for each treatment arm was around 520.

On the other hand, Study 312 was analyzed separately. Compared to Studies 309 and 310, Study 312 did not have the 4-week insulin optimization period or the additional 28-week extension treatment period. Also, Study 312 only had two treatment arms, the sotagliflozin 400-milligram arm and the placebo arm, with a sample size of around 700 per arm.

The efficacy analyses were conducted separately within 3 subgroups defined by baseline eGFR values, the group with eGFR greater than or equal to 90, the group with eGFR between 60 and 90, and the group with eGFR less than 60. The efficacy endpoint of primary interest was A1C change from baseline. Other efficacy endpoints of interest include change from baseline in body weight and change from baseline in systolic blood pressure. Each endpoint was analyzed at week 24, which was

the end of the core treatment period. For the study pool 309 and 310, A1C change from baseline was also analyzed at week 52, which was the end of the extension treatment period.

Baseline characteristics were summarized by subgroups in this table. While the sample size was generally balanced between the group with eGFR between 60 and 90 and the group with eGFR greater than or equal to 90, the sample size for the group with eGFR less than 60 was only around one-tenth of the former two groups. Also, we've noticed that the subjects with eGFR less than 60 were generally older and have a longer duration of type 1 diabetes than subjects from the other two subgroups.

Efficacy analyses were performed on the analysis set consisting of all randomized subjects who took at least one dose of the study drug. Missing data were handled with multiple imputation based on placebo washout, which assumes that effect from the experimental drug was erased for subjects with missing endpoint values. An ANCOVA model adjusted for baseline values, treatment,

stratification factors, and study ID was used for the analysis of each efficacy endpoint.

The next few slides will be presenting the subgroup analysis results on A1C, body weight, and systolic blood pressure. For each endpoint, the results from Study 312 will be presented first, followed by the results from the study pool 309 and 310. This table presented the efficacy result on A1C reduction for Study 312 with respect to the overall population and the three eGFR subgroups. As highlighted in the dashed box, the placebo-adjusted treatment effect was found similar for the overall population, the group with eGFR greater than or equal to 90 and the group with eGFR between 60 and 90. Specifically, all three groups had a point estimate of around negative 0.45 and a confidence interval staying below zero.

On the other hand, as demonstrated in the solid box, the group with eGFR less than 60 had the smallest treatment effect size of negative 0.17 and the widest confidence interval, with an upper bound greater than zero. The discrepancy in the width of

the confidence intervals is due to differences in subgroup sample sizes. Specifically, the group with eGFR less than 60 had only 32 subjects from the sotagliflozin arm and 42 subjects from placebo arm, as opposed to more than 300 subjects per arm from the other two subgroups. The limited sample size resulted in more variabilities and less precision in the estimation of its treatment effect size.

The placebo-adjusted A1C reduction from baseline for Study 312 is further illustrated in this forest plot. Comparing the width of the confidence intervals, we gain a direct sense of the great uncertainties associated with the estimation of the treatment effect size for the group with eGFR less than 60.

This table presented the efficacy result on A1C at week 24 for the study pool 309 and 310. Similar to the results for Study 312, the placebo-adjusted A1C reduction at week 24 for the study pool 309 and 310 was generally consistent between the overall population, the group with eGFR

greater than or equal to 90 and the group with eGFR between 60 and 90. On the other hand, the group with eGFR less than 60 had the smallest treatment effect size and the widest confidence interval due to its limited sample size.

Again, the forest plot here on the placebo-adjusted A1C reduction from baseline provides a direct visualization of the great uncertainties associated with the estimated treatment effect size for the group with eGFR less than 60. In addition, by comparing the two sotagliflozin arms within the same group, we observed that the effect size in A1C reduction was similar between the 400-milligram dose and the 200-milligram dose.

Similar patterns were observed for the A1C results at week 52 for the study pool 309 and 310. Further, we noted that the estimated treatment effect size for each arm at week 52 tends to be numerically lower than that at week 24, suggesting that the drug effect may not be maintained for an extended treatment period.

For the secondary endpoint, body weight change from baseline at week 24 for Study 312, as highlighted in the dashed box, the placebo-adjusted weight reduction from baseline was found generally consistent between the overall population and each of the eGFR subgroups. Specifically, for the group with eGFR less than 60, despite its small sample size, confidence interval for the placebo-adjusted treatment effect stayed below zero just like the confidence intervals for the overall population and the other two eGFR subgroups.

Similar findings can be reported for the body weight results for the study pool 3O9 and 310. Specifically, we see generally consistent treatment effect estimates with confidence intervals below zero for all groups presented in this table, including the eGFR less than 60 group.

For the results of systolic blood pressure for Study 312, as highlighted in the dashed box, the placebo-adjusted treatment effect was generally consistent between the overall population, the group with eGFR greater than or equal to 90 and the

group with eGFR between 60 and 90, all with confidence intervals below zero.

On the other hand, despite a favorable point estimate, the group with eGFR less than 60, as highlighted in the solid box, had the widest confidence interval, with its lower bound going as low as negative 12.27 and upper bound crossing zero. Similar findings can be reported for the study pool 309 and 310. The small sample size and low precision in treatment effect estimate prevent us from deriving any meaningful conclusions for the subgroup with eGFR less than 60.

To summarize, the FDA review of the original NDA submission concluded that the TANDEM program has demonstrated substantial evidence of effectiveness for improving glycemic control in patients with type 1 diabetes. To investigate whether this conclusion holds true for the subpopulation with type 1 diabetes and chronic kidney disease, the FDA utilized a subgrouping strategy with subgroups defined by baseline eGFR values. The estimated treatment effects regarding

A1C change from baseline were found generally consistent for the subgroup with eGFR greater than or equal to 90 and the group with eGFR between 60 and 90.

Smaller treatment effect sizes on A1C reduction were observed in the group with eGFR less than 60. Given the correlation between glucosuria and eGFR, this finding is biologically plausible but the available clinical data are not sufficient to support any definitive conclusions. Furthermore, based on the results from Study 309 and 310, which were designed to evaluate the treatment effect of sotagliflozin 200- and 400-milligram doses at both time points week 24 and week 52, we observed that the effect size in A1C reduction at week 24 appears to attenuate by week 52. Also, we noted that effect size in A1C reduction was similar between the 400-milligram dose and the 200-milligram dose.

Similar trends were observed among the eGFR subgroups; however, the post hoc subgrouping strategy resulted in limited sample sizes,

particularly for the subgroup with eGFR less than 60, and this precludes more definitive conclusions. This is the end of my presentation. Thank you all, and now I will turn it over to Dr. Suzuki.

FDA Presentation - Mari Suzuki

DR. SUZUKI: I am Mari Suzuki. We will now talk about the major safety considerations for sotagliflozin in patients with type 1 diabetes and chronic kidney disease. The safety profile of sotagliflozin was well characterized for patients with type 2 diabetes in two large cardiorenal outcomes trials that supported the approval of sotagliflozin as Inpefa.

The safety profile of sotagliflozin observed in patients with type 2 diabetes was similar to that in the TANDEM program with two notable exceptions. First, sotagliflozin was associated with fewer hypoglycemia events in patients with type 1 diabetes but not in patients with type 2 diabetes. Second, sotagliflozin was associated with a significantly increased risk of DKA in patients with type 1 diabetes but not patients with

type 2 diabetes. For this reason, this presentation will focus on hypoglycemia and DKA.

Hypoglycemia is a common occurrence in patients with type 1 diabetes. Most hypoglycemia events are self-treated but some can be life threatening. The American Diabetes Association categorizes hypoglycemia events according to severity. Level 1 hypoglycemic events involve blood glucose levels less than 70 milligrams per deciliter and greater than or equal to 54. This threshold is an alert value at which patients should take action to avoid decline in blood glucose. A level 2 hypoglycemia event is blood glucose less than 54 regardless of the presence of hypoglycemia symptoms. At this threshold, adrenergic and/or neuroglycopenic symptoms typically begin.

Level 3 is a severe hypoglycemic event characterized by altered mental and/or physical function which, if untreated, may result in loss of consciousness, seizures, coma, or death. A level 3 hypoglycemic event necessitates assistance by

another person for hypoglycemia reversal.

FDA recognizes both level 3 and level 2 hypoglycemia events as acceptable clinical trial endpoints in support of claims related to improve glycemic control, iatrogenic hypoglycemia risk reduction, or both. Level 3 hypoglycemia is a direct measurement of how a patient feels, functions, or survives, and is a clinical endpoint. Level 2 hypoglycemic events are considered to be a surrogate endpoint for neuroglycopenia-related adverse events acceptable for traditional approval.

The TANDEM studies systematically collected hypoglycemia events during the treatment periods. All subjects were provided glucometers and instructed to record every hypoglycemia event in a study diary throughout the entire study period. Dedicated electronic case report forms included elements to record supporting information about the event, including glucometer data, symptoms, and hypoglycemic event severity. Severe hypoglycemic events were adjudicated by a blinded clinical events committee. These studies were designed

prior to the ADA's definition of hypoglycemia.

For purposes of the review of NDA 210934, FDA considers the applicant's prespecified definitions of blood glucose less than or equal to 55 and of severe hypoglycemia to be sufficiently consistent with FDA's preferred definitions of level 2 and level 3 hypoglycemia events.

To assess safety from the perspective of hypoglycemic risk for the current submission, FDA reanalyzed the hypoglycemia data from the TANDEM program according to eGFR subgroups to assess whether similar patterns would occur across the range of eGFRs proposed for the revised target population. First, we'll discuss level 3 hypoglycemia events.

This table shows the incidence and total events of level 3 hypoglycemia that occurred in the TANDEM program during the full study period. The first row shows Study 309 and 310. The second row shows Study 312. Level 3 hypoglycemia was analyzed by the incidence of events and by the total occurrences. The analyses were conducted across

studies and doses. There was not a consistent trend across the studies, treatment arms, or summary statistics in level 3 hypoglycemic events. Inspection of these results, according to eGFR category, did not reveal any additional insights.

Now, let us turn to the level 2 hypoglycemic events. Over 90 percent of subjects in each treatment arm experienced at least one level 2 hypoglycemic event. For this reason, we focused on the event rate ratio for level 2 hypoglycemia rather than the incidence of level 2 hypoglycemic events. The data show that sotagliflozin treatment was associated with a 14 to 24 percent reduction in the event rate ratio of level 2 hypoglycemia among participants in the TANDEM studies.

This table shows event rate and event rate ratio for placebo and sotagliflozin-treated arms, going left to right, for studies 309 and 310, and then Study 312, and going top to bottom by eGFR subgroups. As was observed in the overall population, sotagliflozin was associated with reduced risk of level 2 hypoglycemia events in each

eGFR subgroup. The reduction in risk was consistent across studies, and the magnitude of reduction was similar for sotagliflozin 200 milligrams and sotagliflozin 400 milligrams.

Although level 2 hypoglycemia was not an endpoint subject to formal statistical testing, the observed reduction in level 2 hypoglycemia risk is both numerically robust and biologically plausible, as participants randomized to sotagliflozin reduced their use of exogenous insulin during the trial. In aggregate, these data suggest that sotagliflozin treatment at either 200 milligrams or 400 milligrams in patients with type 1 diabetes and mild to moderate CKD may reduce the risk of level 2 hypoglycemic events.

Diabetic ketoacidosis, or DKA, is a serious life-threatening metabolic complication that requires immediate medical intervention. Although DKA traditionally presents with hyperglycemia, DKA events associated with SGLT2 inhibitor use sometimes present as euglycemic DKA, that is, DKA with normal blood glucose concentrations. All

approved SGLT2 inhibitors, including sotagliflozin marketed as Inpefa, have similar warnings and precautions in their labeling regarding the risk of DKA. An increased DKA risk has been demonstrated in randomized clinical trials of multiple SGLT2 inhibitors in patients with type 1 diabetes.

The proposed pathophysiology of SGLT2-associated diabetic ketoacidosis is shown here. SGLT2 inhibitors cause a lowering in plasma glucose levels, which lead to a reduction in exogenous insulin dose. This causes a shift in metabolism to lipolysis and ketogenesis in the liver. SGLT2 inhibitors also increase the renal reabsorption of ketone bodies, thereby increasing plasma ketone levels. Some studies suggest that SGLT2 inhibitors may have direct stimulatory effects on the pancreatic alpha cells, causing an increase in plasma glucagon levels. SGLT2 inhibitors also decrease sodium reabsorption, resulting in volume depletion, which may compound on the risk for DKA.

This table displays the statistical results

for DKA in the overall type 1 diabetes population. This analysis pooled the 200-milligram and 400-milligram doses of sotagliflozin for Studies 309 and 310. The rightmost column reports the number of person-years of treatment with sotagliflozin needed to incur one DKA event, 31 patient-years in Studies 309 and 310 and 20 patient-years in Study 312. Participants in Studies 309 and 310 underwent insulin optimization during the run-in period, which may explain the lower overall DKA event rates observed compared to the overall rates of DKA observed in Trial 312.

During the conduct of the TANDEM studies, additional risk mitigation strategies were introduced, but the data did not support a conclusion that the strategies meaningfully reduce the increased risk of DKA associated with sotagliflozin. The vast majority of the events of DKA observed in the TANDEM program required hospitalization, and many required ICU management. These data represent the basis of FDA's unfavorable benefit-risk assessment for sotagliflozin for the

original submission of NDA 210934.

Because Trials 309 and 310 randomized participants to placebo, sotagliflozin 200 milligrams, or sotagliflozin 400 milligrams, FDA assessed the evidence of a dose-response relationship for DKA. The figure above shows days since first dose on the X-axis and cumulative incidence of DKA on the Y-axis. The line in blue is sotagliflozin 400 milligrams, green is sotagliflozin 200 milligrams, and red is placebo. DKA events continued to accumulate steadily throughout the trial for both dose strengths of sotagliflozin. The cumulative incidence of DKA in the overall 309 and 310 population suggests the dose-response relationship for sotagliflozin administered as 200 milligrams or 400 milligrams, and DKA.

We include the statistical estimates for number needed to harm, or NNH, for each dose category to the right of the plot. Although the confidence intervals for the number needed to harm overlap for the 2 doses, a numerically greater risk

was observed with sotagliflozin 400 milligrams compared to sotagliflozin 200 milligrams.

Similar to our analyses regarding efficacy and hypoglycemia endpoints, we reanalyzed the DKA data from the TANDEM program according to eGFR subgroup. As was observed in the overall population, sotagliflozin was associated with an increased risk of DKA in each eGFR subgroup. The graph presents a forest plot of the incidence rate differences between participants randomized to sotagliflozin versus placebo. Pooled Studies 309 and 310 are displayed at the top of the graph and Study 312 is displayed at the bottom.

Estimates of DKA risk for each eGFR subgroup are presented. The error bars represent the 95 percent confidence interval of each estimate. To the right of the graph, we present the corresponding number needed to harm per patient-year and the associated 95 percent confidence interval.

The subgroups with an eGFR between 60 and 89 and greater than 90 appears generally consistent

with the overall estimate, but it is notable that the confidence intervals are wide and overlapping. The subgroup for eGFR less than 60 appears to have the largest increase in DKA risk; however, this should be interpreted with caution because only three DKA events occurred in this subgroup in Study 309 and 310, and only one event occurred in the subgroup in Study 312.

Due to the paucity of clinical trial data available to inform the risk of DKA in subjects with type 1 diabetes and chronic kidney disease, FDA considered epidemiologic studies to further inform the DKA risk in the type 1 diabetes and chronic kidney disease population. FDA considered three additional data sources: the Finnish Diabetic Nephropathy Study, also referred to as FinnDiane; FDA queried the Sentinel system, which is an active surveillance system maintained by FDA to monitor the safety of medical products using existing healthcare data from multiple sources; and finally, FDA considered a post hoc analysis of the T1D exchange submitted by the applicant.

FinnDiane was a registry study that investigated the risk of hospitalization for DKA in 4,758 adults with type 1 diabetes enrolled between 1994 and 2015 in Finland. At baseline, 547 participants had an eGFR less than 60. During a median follow-up for 14 years, 969 non-fatal or fatal events of hospitalization for DKA were ascertained. The study found that participants with baseline eGFR less than 60 had a 1.7-fold increased risk of hospitalization for DKA adjusted for prior history of hospitalization for DKA; insulin pump use; smoking; weekly alcohol consumption; serial A1C; A1C variability over time; high-density lipoprotein level; and triglyceride level compared to participants with a baseline eGFR greater than 60.

The authors concluded that the presence of CKD can serve as a predictor for DKA events in patients with type 1 diabetes, and that this may have implications for the use of SGLT2 inhibitors in patients with type 1 diabetes and chronic kidney disease.

FDA's Sentinel analysis evaluated claims data from 2013 to 2024 from six data partners for crude incidence rates of DKA in patients with type 1 diabetes and chronic kidney disease. DKA was identified by matching to a prespecified list of ICD codes suggestive of DKA. Type 1 diabetes and CKD stage were identified using adaptations of published and validated algorithms. The descriptive data from the Sentinel distributed database suggests that patients with type 1 diabetes with a diagnosis of advanced CKD have a greater risk of experiencing DKA than patients with type 1 diabetes without a diagnosis of CKD.

The T1D Exchange is a multicenter, electronic, medical record database. Between 2015 and 2023, 1,558 patients with type 1 diabetes and CKD and 47,620 patients with type 1 diabetes without CKD were identified in T1D Exchange. Over a mean 5.2 years of follow-up, the applicant identified DKA events in 117 of 1,558 patients with type 1 diabetes and CKD and in 3,652 of 47,620 patients with type 1 diabetes without CKD, which

corresponded to 2.9 and 3.2 events per 100 person-years, respectively. These results are incongruent with the Sentinel analysis, which suggested that patients with type 1 diabetes and CKD have a greater risk of experiencing DKA than patients with type 1 diabetes without CKD.

The applicant also created propensity score matched cohorts of patients with type 1 diabetes with CKD and patients with type 1 diabetes without CKD. The DKA rate was numerically greater in type 1 diabetes with CKD than in propensity score-matched patients with type 1 diabetes without CKD.

In summary, two of three epidemiology studies suggest subjects with CKD might have an increased baseline risk of DKA. These data cannot determine whether CKD is an independent risk factor or a proxy for other correlated risk factors for DKA, nor can these data directly inform sotagliflozin-related risks; however, drug-related risks might be higher in a more vulnerable population. Although limited, these data raise

some uncertainties about the generalizability of estimates of DKA risk from the overall TANDEM population to patients with type 1 diabetes and CKD.

Summarizing safety findings, sotagliflozin reduced the event-rate ratio of level 2 hypoglycemia. A similar effect was observed in the overall population and each eGFR subgroup. A similar trend was not seen in level 3 hypoglycemic events. Sotagliflozin increased the risk of DKA. The effect was observed in each eGFR subgroup, but the data are too limited to make conclusions about an interaction between eGFR and sotagliflozin on DKA risk. The data are particularly limited for subjects with an eGFR below 60. Epidemiologic data raise uncertainties about the generalizability of estimates of DKA risk in TANDEM to patients with type 1 diabetes and CKD.

I will now turn it over to Dr. Justin Penzenstadler.

FDA Presentation - Justin Penzenstadler

DR. PENZENSTADLER: Good morning. My name

is Justin Penzenstadler, and I'm a clinical team leader in the Division of Diabetes, Lipid Disorders, and Obesity, and the cross-discipline team leader for this application. My presentation will cover an integrated summary of FDA's review findings for sotagliflozin.

This is the outline for my presentation. First, we will review the reductions in A1C observed in TANDEM and in TANDEM subgroups. I will touch on the magnitude and durability of the reductions in A1C and provide some context for the clinical benefit of this A1C reduction for patients with T1D and mild to moderate CKD.

Next, we will discuss the additional advantages of sotagliflozin. This will include a discussion on hypoglycemia, body weight, and systolic blood pressure; then we will go over the potential benefits beyond glycemic control for patients with T1D and CKD as suggested by the SCORED study. Last, I will discuss the increased risk for DKA.

Evidence for the effectiveness of

sotagliflozin to improve glycemic control was demonstrated in the overall TANDEM population. The results of that analysis are presented in the first row of this table. Both the FDA and the applicant conducted some post hoc analyses to investigate the A1C lowering effect of sotagliflozin in patients with T1D and CKD. The results of this analysis are provided in the second row. For reasons discussed by Dr. Suzuki, this approach may overestimate the treatment effect in patients with an eGFR less than 60.

The FDA subgroups are presented in the last three rows. The main advantage of the FDA approach is that it provides different estimates of treatment effect for different subgroups of eGFR. We thought this was important given the dependence of drug effect on GFR. Both approaches returned results that generally support a conclusion of efficacy at week 24.

Participants in Study 309 and 310 were optimized on insulin and had a relatively low baseline A1C of 7.7. This may explain the smaller

reduction in A1C in Study 309 and 310 compared to Study 312. Our analysis suggested a smaller reduction at week 24 for patients with an eGFR less than 60, but it is difficult to draw conclusions due to the sample size, which was about 5 percent of the overall TANDEM population.

The results at week 52 raised concerns about the durability of the A1C lowering effect regardless of analysis approach. Putting aside the uncertainties about the magnitude and durability of the A1C lowering effect, FDA reviewed the available literature to contextualize the meaningfulness of A1C reductions in patients with T1D and CKD. The Diabetes Control and Complications Trial, or DCCT, demonstrated that a sustained improvement in A1C reduces the risk of microvascular complications in patients with T1D; however, participants in DCCT had a mean age of 27 years, a mean duration of diabetes of 6 years, and a preserved eGFR trial entry which limits the applicability to patients with T1D and CKD.

The Preventing Early Renal Loss in Diabetes

Study, or PERL, investigated whether urate lowering therapy improves renal outcomes in patients with T1D and mild to moderate CKD. The participants in PERL were randomized to allopurinol or placebo, and followed for 3 years. The PERL population closely resembles the revised target population proposed by the applicant. Summary values of eGFR and proteinuria are circled in blue on this slide. PERL participants had a mean age of 51 years, a mean A1C of 8.2 percent, a mean diabetes duration of 35 years, and a mean UACR of 41. Post hoc analyses conducted on PERL indicate that improved glycemic control in patients with T1D and mild to moderate CKD slows the rate of decline of eGFR.

FDA also considered findings from the Joslin Proteinuria Cohort, which was a cohort of patients identified based on the presence of macroalbuminuria. A retrospective analysis of this cohort also showed a correlation between improvements in A1C and better renal outcomes. In the Joslin Proteinuria Cohort, the median UACR was 687 and the median eGFR was 85.

We thought PERL is the most relevant to assess the meaningfulness of A1C reductions in patients with T1D and mild to moderate CKD. Over the three-year study, participants experienced an average eGFR decline of 2.5 milliliters per minute per year. A linear mixed effects model applied to these data quantified the association between A1C and eGFR decline.

This effect appears to be modest. The model, which included all significant patient features identified from univariate tests, predicts that a 1 percent improvement in A1C would reduce the eGFR decline by 0.54 milliliters per minute per year. This suggests that a 0.3 to 0.4 percent reduction in A1C sustained over 10 years might translate to a preservation of 1.6 to 2.4 milliliters per minute in eGFR in a patient with T1D and mild to moderate CKD.

The figure presented in this slide presents the model-based estimates of eGFR decline by degree of proteinuria and A1C level. The Y-axis is the rate of eGFR decline and the X-axis includes

categories of proteinuria and A1C. The different colored point ranges represent levels of glycemic control. Within each proteinuria group, worsening glycemic control was associated with more rapid decline in eGFR. This figure also suggests that the benefit of A1C reduction might be more substantial in patients with macroalbuminuria.

Evidence that improved glycemic control confers greater benefit to patients with T1D and macroalbuminuria was also suggested by a retrospective analysis of the Joslin Proteinuria Cohort. A multivariate Cox regression analysis suggested that a 1 point improvement in A1C reduced the risk of progressing to end-stage renal disease by 24 percent over a median follow-up of 5 years.

A distinguishing characteristic of sotagliflozin in patients with T1D is that it improves glycemic control while also reducing the risk of hypoglycemia. Although we did not see a clear trend in level 3 hypoglycemia, a consistent reduction in level 2 hypoglycemia was observed across trials and eGFR subgroups in the TANDEM

program. This association is biologically plausible. Exogenous insulin is responsible for hypoglycemia in patients with type 1 diabetes, and participants treated with sotagliflozin reduced their insulin dose during the study.

Now, quantifying this benefit had some challenges. Although FDA acknowledges level 2 hypoglycemia as a surrogate endpoint for neuroglycopenia-related adverse events, it's not obvious how to weigh a 20 percent reduction in the risk of such events against the less frequent but more clinically significant occurrence of DKA. While the reduced insulin dose likely contributed to the hypoglycemia advantage, it also may have contributed to the increased DKA risk.

This table presents the results for placebo-adjusted changes from baseline and systolic blood pressure in the first row and body weight in the second row for pooled studies 309 and 310, and separately studied 312. The results broken down by eGFR subgroup are not displayed because the overall treatment effects were generally consistent with

the overall estimates displayed here. Though modest, the effect on systolic blood pressure, about 2 to 3 millimeters of mercury, and the effect on body weight, 2 to 3 kilograms, might be considered an advantage of sotagliflozin; however, not all patients require blood pressure lowering or weight loss. In the population studied, the baseline systolic blood pressure was approximately 123 millimeters of mercury and the baseline body weight was approximately 85 kilograms.

Now, let us turn to the potential benefits beyond glycemic control suggested by the SCORED study conducted in patients with type 2 diabetes, moderate to severe CKD, and other cardiovascular risk factors. An important question for this committee is how the findings of SCORED applied to patients with mild to moderate CKD and type 1 diabetes. SCORED demonstrated a reduced risk for the composite endpoint of CV death, hospitalization for heart failure, and urgent heart failure visits. SCORED suggested other potential benefits such as a reduction in the progression of kidney disease and

reduction in major adverse cardiovascular events or MACE.

There are significant uncertainties when extrapolating benefits from SCORED to patients with T1D and mild to moderate CKD. The SCORED population differs from patients with T1D and mild to moderate CKD beyond differences in the pathophysiology underlying their diabetes. Participants in SCORED had moderate to severe CKD. About half of the participants had an eGFR less than 45, and about one-third had a UACR greater than 300.

Importantly, the magnitude of absolute benefits observed in SCORED were greatest in participants with more severe kidney disease. Thus, even if the benefits suggested in SCORED apply, the magnitude of those absolute benefits are not likely to be preserved in patients with mild to moderate CKD. Similarly, one must consider that the median age in SCORED was 68, the median BMI was 32. Thirty-one percent of participants had a history of heart failure, 20 percent had a history

of myocardial infarction, and 22 percent had a history of coronary revascularization. We do have a slide and backups prepared, which compares the demographics of SCORED and the TANDEM CKD subpopulation. Finally, SCORED did not demonstrate a statistically significant benefit on MACE or the progression of kidney disease, so we consider these potential benefits rather than demonstrated benefits.

This figure is adapted from the package insert for Inpefa. It shows a subgroup analysis for the primary endpoint of SCORED grouped by baseline. eGFR. The hazard ratio, a relative measure of benefit, appears consistent across eGFR categories. We have less than 30, 30 to 45, and 45 to 60. On the right of the figure, I have annotated the number needed to treat calculated by taking the difference in event rates between sotagliflozin and placebo.

The absolute measure of benefit across these subgroups is correlated with eGFR, with the eGFR group of 45 to 60 showing the least absolute

benefit. In SCORED participants with eGFR 45 to 60, the number needed to treat is approximately 83 person-years for sotagliflozin to prevent one additional event of hospitalization for heart failure, CV death, or urgent heart failure visit. Patients with mild to moderate CKD might be expected to have an even lower benefit if this trend continues. Ultimately, it is unknown what benefits might accrue to patients with T1D and mild to moderate CKD.

Now, I will briefly summarize the findings from SCORED in the context of the DKA risk observed in TANDEM. SCORED demonstrated a reduced risk for the composite endpoint of CV death, hospitalization for heart failure, and urgent heart failure visit. Among patients with T2D, eGFR 45 to 60, and other cardiovascular risk factors, the number needed to treat is approximately 83 person-years for sotagliflozin to prevent one additional event.

SCORED suggested a potential reduced risk in a renal composite. Among patients with type 2 diabetes, baseline eGFR 45 to 60, and other

cardiovascular risk factors, the number needed to treat is approximately 250 person-years for sotagliflozin to prevent one additional renal event. SCORED suggested a potential reduced risk in MACE. For the entire SCORED population, the number needed to treat is approximately 90 person-years to prevent one additional event of MACE.

These observations seem reasonable to consider in a benefit-risk calculus for the proposed revised indication, but it is unclear how much weight they should be given. The magnitude and uncertainty of these benefits should be considered in the context of the observed DKA risk and uncertainties extrapolating any of these estimates to a largely unstudied population of patients with T1D and CKD.

Regarding DKA, the estimated number needed to harm is approximately 20 to 30 person-years for sotagliflozin to cause one additional DKA event in the overall population. None of the events observed in TANDEM were fatal, but most events

resulted in prolonged hospitalization, with many requiring admission into an intensive care unit. The DKA risk appears to be dose related and the DKA risk also appears to accumulate steadily over time. The data were too limited to provide meaningful conclusions on the relationship between drug and DKA risk across the CKD stage, particularly for patients with an eGFR less than 60.

Even if risk of a DKA event is the same in the revised target population, the clinical consequences of the event could be different. Authors from the CDC analyzed the case fatality rate of in-hospital DKA events in U.S. patients with type 1 or type 2 diabetes. This table from the study shows that the case fatality rate increases steadily with age, as is evident by the rates reported for the different age groups in the red boxes.

This finding is not surprising given the comorbidities experienced by older patients with diabetes, but it is relevant. Patients with type 1 diabetes selected for treatment with sotagliflozin,

because of the presence of mild to moderate CKD, will likely be older than the participants studied in TANDEM. Although age is a poor proxy for chronic kidney disease, it illustrates how indicating sotagliflozin for a population different than the one studied introduces uncertainty.

Available epidemiology data do not provide reassurance that the magnitude of the DKA risk observed in TANDEM applies to patients with T1D and CKD for either incidence or severity. Similar findings with sotagliflozin could be realized in the postmarket setting, where patients would not be followed as closely as they are in a clinical trial setting. Finally, mitigation strategies to reduce the risk of DKA postmarketing have not been tested in premarketing studies. This concludes my presentation. Thank you for your time and attention, and I look forward to the discussion.

Clarifying Questions to FDA

DR. LOW WANG: Thank you.

We will now take clarifying questions for the FDA. 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 of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

So asking the panel, are there any clarifying questions for the FDA? Let's start with Dr. Wang.

DR. WANG: Thanks. Thomas Wang. I appreciate the FDA's presentation. I'm just trying to reconcile some of the interpretive differences between the sponsor and the FDA. In the sponsor's presentation, there was a comment -- I think it was in Dr. Davies' presentation -- that there was an improved risk-benefit profile in the T1D-CKD subpopulation compared to the overall T1D subpopulation.

I think that was based on the level 2

hypoglycemia results because I think both sides seem to acknowledge that the A1C reduction seems comparable in the overall versus the CKD population, and the DKA risk may be comparable or certainly not improved. So I guess that leaves us with hypoglycemia. Again, both the FDA and the sponsor seem to agree that there's really no difference in the level 3, so that gets to the level 2.

I guess the question for the FDA, and maybe referring to slide 50, with level 2 hypoglycemia, is it your conclusion that when you compare the overall population to the CKD subpopulation, that, more or less, the reduction in hypoglycemic episodes is similar?

DR. PENZENSTADLER: Thanks for the question, Dr. Wang. Yes, that's how we feel about it. Most of our exercises with these data are to look at the overall estimate, and then check for consistency in the CKD subgroups. We did inspect the overall treatment effects for hypoglycemia among the overall TANDEM, and then we noticed that the

subgroups of 90-plus and 60 to 89 were consistent with that estimate. It's a similar story for most of the other benefits and risks we looked at; 60 to 89 and 90-plus were generally consistent, and there was not enough data in the less than 60 category. Thank you.

DR. ARCHDEACON: If I can jump in as well -- Patrick Archdeacon -- as Justin is saying, I don't think we actually think that the hypoglycemia is different for the overall population in the various CKD subgroups. I think where we understand the applicant's position, I think we're suggesting that although our analyses of A1C suggests some uncertainty for the eGFR less than 60, we would acknowledge that there appears to be evidence, in general, of similar A1C reduction certainly above 60.

I think what they're suggesting is for a similar A1C reduction, a patient who has established chronic kidney disease would get a greater benefit, and I think the argument is that somebody who does not have established kidney

disease has a lower risk of progressing. So for the same A1C reduction, the clinical benefit is greater.

Was that clear?

DR. WANG: No, that is clear, and I recognize there the non-glycemic benefits that are part of the discussion. But I at least want to establish for the glycemic benefits that the risk-benefit profile, there's clear evidence that it's better.

DR. ARCHDEACON: In addition to the non-glycemic, I think what we tried to illustrate with the PERL study, for instance, we acknowledge that there was some evidence that patients who have established kidney disease, that if you improve their A1C -- now, keep in mind this is an observational study interpretation of some data, but there is some reason to think that controlling their A1C slows the progression of the kidney disease. For instance, that benefit was greater in people who had a UACR greater than 300 compared to those with a UACR 30 to 300.

So I think what we're suggesting is the glycemic benefit can confer a greater clinical benefit depending on how much proteinuria you have and what your baseline eGFR is.

DR. WANG: Yes, understood.

DR. ARCHDEACON: Okay.

DR. LOW WANG: Next, Dr. Everett.

DR. EVERETT: Thanks. Brendan Everett, and two clarifying questions on different slides for the FDA, maybe since we were just talking about the PERL study, slide 66. We had some conversations earlier about this observed statistically strong relationship and association between baseline levels of A1C and outcomes, whether they be micro or macrovascular, so a question about whether or not actually treating that intermediate, or as a value goal for treatment of hemoglobin A1C, is this the baseline A1Cs and the association, then, with outcome, or is this actually an intervention where we're looking at changes?

It talked a lot about changes in A1C, but I think this is just an association analysis based on

A1C; right?

DR. PENZENSTADLER: That's correct, Dr. Everett.

DR. EVERETT: Okay. So we don't actually know, in this population, what an intervention targeted at A1C would do to the risk of kidney outcomes.

DR. PENZENSTADLER: That's also correct.

DR. EVERETT: Okay. Thank you.

The other clarifying question is for slide 58, which was from the Sentinel query. I think it's labeled Crude Incidence Rates. So I'm presuming that these are not adjusted, or propensity matched, or any any effort to try and find similar patients who have different levels of kidney disease at baseline.

DR. PENZENSTADLER: That's correct.

DR. EVERETT: Okay. Great. So there's potentially residual confounding here.

DR. PENZENSTADLER: Yes, and I'll invite our epidemiologist to provide input as well. Thanks.

DR. CHANG: Po-Yin Chang, Division of

Epidemiology. This slide shows here the crude analysis results, and we don't adjust for any potential confounding factors. The ongoing analysis, we are looking at adjusted results for Sentinel analysis here.

DR. LOW WANG: So just a quick question about this slide, if the FDA could clarify the definition of type 1 diabetes. Was this the broad or the narrow category?

DR. CHANG: So there's a discussion about how we can identify type 1 diabetes using claims data. In previous studies, there have been some validation studies about how we can use the diagnosis of type 1 diabetes and diagnosis code of type 2 diabetes to define the type 1 diabetes population. In these Sentinel studies, we modify the previous algorithm to identify the type 1 diabetes population. They are potentially after we use type 2 diabetes treatment, so we further narrow the definition of type 1 diabetes algorithm, so we exclude people who have used potential type 2 diabetes optimal treatment for type 1. So here,

we've shown the most strict definition of type 1 diabetes in Sentinel using claims data.

DR. LOW WANG: Great. Thank you.

Dr. Konstam?

DR. KONSTAM: Yes. Thanks. Marv Konstam, a general question and then a specific question. A general question is, we need to try to figure out benefit-risk ratio, which is a little difficult when you don't exactly know what the benefit is and you don't exactly know what the risk is. But I wonder, despite that, whether you made any attempt to model potential risk-benefit, quantitative risk-benefit relationships, based on some assumption of DKA, for example, versus some assumption of improved kidney function.

If we assume certain levels of those two, and the sensitivity analysis around that, what would that risk-benefit ratio look like? And the more specific -

DR. LOW WANG: Dr. Konstam, we can't quite hear you; if you could speak a little closer.

DR. KONSTAM: Did you hear me?

(No audible response.)

DR. KONSTAM: Okay.

Secondly, with regard to your slide 73, you mentioned a number needed to harm with DKA being approximately 20, and this is based on the sponsor's studies; is that that correct, in terms of the DKA rate? What is it, if you use your Sentinel data set to estimate the real-life likelihood of DKA events?

DR. PENZENSTADLER: Okay. I heard two questions there. Maybe I'll tackle the first one, and then I'll direct the second one to Dr. Po-Yin Chang. The first question was, did the FDA embark on quantitative benefit-risk analyses considering the DKA risk versus renal endpoints such as end-stage kidney disease and so on?

We did. We thought about it. What we ended up discovering as we looked into the data further is that the literature is very sparse, and it's particularly challenging to extrapolate these findings in TANDEM. There are lots of assumptions that need to be made to give any meaningful

quantitative benefit-risk assessment, and we ultimately decided we didn't have enough data that was meritus to present here.

As for your second question --

DR. CHANG: Can you please clarify the second question?

DR. KONSTAM: The question, from your slide 73 -- maybe you want to put it up -- you estimate the number needed to harm for DKA is approximately 20, and I guess that's based on the sponsor's trials estimates of DKA rates. I wonder what that number goes to if you use the Sentinel data, which in my mind might be more realistic about the amount of DKA you're likely to see.

DR. CHANG: Po-Yin Chang, Division of Epidemiology. To estimate a number needed to harm in Sentinel, we need to have the comparator groups for SGLT2 inhibitors, but we don't have that in our Sentinel analysis right now, because an exposure group and a comparator's group in a trial is placebo.

DR. KONSTAM: Yes. Well, here the

comparator group would be patients with DKA without sotagliflozin, I guess, and we believe that number would be really low in terms of the rate of DKA, in general, in type 1 diabetes, in the absence of an SGLT2 antagonist.

DR. CHANG: Right now what we have from Sentinel is descriptive analysis result. We don't have any comparative analysis result yet. The analysis is ongoing, so we might have that in the future.

DR. KONSTAM: Okay. Thank you.

DR. LOW WANG: Alright.

Next, Mr. Tibbits.

MR. TIBBITS: Thank you. Paul Tibbits. Certainly, this is a data-driven exercise, but this question, I think, gets away, a little bit, from the data, so I'll open up to whoever wants to respond.

So having lived with diabetes for 44 years now and reading the public comments in the docket, for years we're told that lowering A1C is a good thing, writ large, for multiple reasons. It

reduces the risk of multiple complications. So certainly now we're looking at data for people with type 1 that have reduced levels of eGFR, reduced kidney function, potentially. So I understand the focus of A1C and its potential impact on eGFR, but I guess as a patient with diabetes, and maybe one with impaired kidney function, I'm still thinking about other complications.

So it seems like the FDA's presentation, in some ways, is that, yes, we acknowledge there's an A1C impact, but that's not actually good enough. We need to have a demonstrated A1C impact that has a demonstrated clinical benefit on this particular kidney function. I mean, again, as a patient, that seems like a little bit of moving the goal posts, saying, "Well, this reduction in A1C isn't quite good enough. You need to reduce A1C plus something else," even though there are -- and admittedly, these trials, these other complications have potential impact on other complications, but as patients, we're looking for ways to reduce A1Cs. It sounds a little bit like that by itself is no

longer enough.

DR. ARCHDEACON: I think the reason we're holding the committee is to have the discussion. I think what we would say is, certainly, if there was a product that did not have a significant risk, then A1C by itself would certainly be enough.

I guess to also try to address you, Dr. Konstam, the concern, I think, is if we're talking about a 1 in 20 person-year or 1 in 30 person-year for an additional case of DKA, I think a reasonable estimate of the case mortality rate of DKA might be around 1 percent. So we'd be thinking it would approximately be 2000 to 3000 person-years to cause a death. I think that's why we're pausing now and saying is A1C alone enough? Because it's hard to quantify what a 0.3 percent reduction would translate to in number of lives saved. I think there probably is some number, but I don't know what that number is. So I think that's what we're trying to get from this committee to help us struggle with that. Certainly if we weren't talking about a death for every 2000

patient-years, there'd be no problem with accepting A1C.

DR. KONSTAM: May I say, my understanding over the years is that glycemic control you view as a surrogate sufficient for approval because it's so clearly linked to microvascular events, and not because of a clear relationship with major cardiovascular events or renal events.

DR. ARCHDEACON: That's correct. That's the basis. In DCCT, the primary readout there is retinopathy, which is treatable; nephropathy, but certainly nephropathy ultimately will progress to end-stage kidney disease in some number of people, and certainly mortality is increased in people who are on dialysis. So we don't mean to negate that in some way A1C must translate to significant clinical benefit. What we're just trying to figure out is how much a 0.3 percent or 0.4 percent reduction, if sustained, what magnitude of clinical benefit can we figure out to attach, then, to counter what we're concerned about, which I think really is this potential in terms of increased

deaths, ultimately.

DR. PENZENSTADLER: Dr. Yanoff?

DR. YANOFF: I wanted to just add one quick thing. Paul, you were probably not at the original advisory committee, and I think your question may be due to the approach we're taking to present this a second time from a different context rather than de novo. The first time this was presented, we kind of took the approach you're thinking, A1C versus DKA; A1C is enough. It's not that A1C isn't enough; it's that our decision was that the benefit that would be accrued by that A1C reduction -- which was going to be small, maybe 0.3 percent, maybe 0.2 percent at the end of 52 weeks -- didn't outweigh the DKA risk.

What we're asking today is, if you already have chronic kidney disease, that 0.2 percent, if we all agree that that has been demonstrated, does that mean something more? It's still A1C is still enough. It's just that the applicant is suggesting that this population that has been divided out from their original proposal would get more out of that

A1C reduction than the overall population, and that perhaps might be enough to outweigh the DKA risk.

DR. LOW WANG: Okay. Dr. Parsa?

DR. ARCHDEACON: The final thing I'd say, too, is we are here asking your opinion on that question. I think we're trying to come up with what our opinion ought to be, and that's why we're asking you to help us inform our opinion.

DR. LOW WANG: Dr. Parsa?

DR. PARSA: Great. I have two questions and then comments, one related to risk --

DR. LOW WANG: And if you could state your name.

DR. PARSA: Oh, sorry. Afshin Parsa. I have two separate questions, one related to risk and one related to benefit, where I think both might in some ways be greater than presented based on the TANDEM and SCORED data.

Regarding risk, DKA obviously increased risk quite a bit more. Now, in the trials, the baseline risk for DKA was around 1 percent in the placebo group, but of course that's short time in a select

group of participants who enrolled in a study, have a relationship, and trust their physicians, and so on, and not taking it chronically. In the claims data, the baseline DKA was higher, so that would then presumably really increase the risk of DKA with this and if one is to infer potential over long term greater than what was implied in the studies.

Is that something that you generally find, where the claims data captures long-term risk better? I know those are still not complete in its claims data, but what's your perspective on that?

DR. PENZENSTADLER: Thanks for the question, Dr. Parsa. I'll ask Dr. Po-Yin Chang from the Division of Epidemiology to respond.

DR. CHANG: Po-Yin Chang, Division of Epidemiology. From what I'm hearing is the risk of DKA is lower in clinical trial, but it seems like the risk of DKA is higher in claims data. We have this discussion about whether we can compare the trials data to claims data. I believe in the first AC meeting, we have that estimation using trials

data, and look at if the trials data were similar to the claims data population, what the risk would look like. We don't have that this time in the current FDA Sentinel query because one major assumption is the baseline characteristic has to be the same between trials population and claims data population. We don't have the data for now, so that's one reason.

Secondly, claims data has its limitations. For example, we could have a potential false positive of DKA, but we are using a validated claims algorithm to identify hospitalization for DKA. The positive predictive value of that algorithm is between 70 to 90 percent. There are only two studies looking at the positive predictive value of this algorithm. It's not perfect, but that's the limitation of the claims data. Partly, that can also explain why we have a higher risk of DKA in claims data compared to trials data. Thank you.

DR. PARSA: Thank. Afshin Parsa, question number --

DR. LOW WANG: Yes, go ahead.

DR. PARSA: -- number two, obviously, what's changed, as Dr. Yanoff said, from prior to now is the potential benefit for cardiorenal and other factors, apart from the improvement in glycemic control, yet, all the data we're seeing, still, really, improvement in glycemic control are not part there. We have the data from SCORED but, really, I mean, one is thinking about class benefit, in other words empa, and dapa, and the other studies. And if then one looks at those, where the benefits were both in individuals with type 2 diabetes and without diabetes, then personally I'm certainly much more comfortable inferring that those would relate to type 1 diabetics because it's quite a broad spectrum, but we have not discussed or said anything about the other SGLT2 inhibitors.

Is a class effect something that the FDA takes into consideration? I know there are always some differences, and this is SGLT1 and 2.

DR. ARCHDEACON: I think I mentioned in my

opening talk that empagliflozin and dapagliflozin have now been approved for the treatment of chronic kidney disease. And if you read the labels of those, those labels would apply to patients with type 1 diabetes. So those products do have an approval that does encompass patients with type 1 diabetes and chronic kidney disease. From our point of view, we need to consider the data that is within this NDA, so I would turn to the sponsor if they wanted to address the question about their regulatory approach.

DR. LOW WANG: Dr. Yanoff?

DR. YANOFF: I apologize if there's a misunderstanding of your question, but based on your question, I'm wondering if there's still some confusion about what we mean by glycemic control and what we mean by renal benefit. We do believe that improving glycemic control will improve kidney outcomes by reducing the risk of microvascular disease, but there are other renal benefits that this class of drug has shown that we don't know -- I don't know what the mechanism is, but

it's not through glycemic control because, as Dr. Archdeacon just said, two members of this class have been approved to reduce the progression of CKD in patients without diabetes.

What is on the table today is deciding whether the A1C reduction and the reduction in microvascular diabetic kidney disease is more important than someone who already has kidney disease. The issue of other non-glycemic benefits that have not been demonstrated for sotagliflozin but have been demonstrated for other classes, hopefully we won't be going in that direction in this discussion, but we can consider the non-glycemic benefits in the SCORED study and how relevant you think they are to what is being proposed, which is to improve glycemic control, not to improve kidney function.

DR. PARSA: Thank you.

DR. LOW WANG: Dr. Everett?

DR. EVERETT: Thank you. Brendan Everett. This is actually perhaps related a little bit. We have, I think, consensus, broadly, between the FDA

and the manufacturer, that in patients with an eGFR less than 60, that this medication leads to a reduction in level 2 hypoglycemic events; a reduction in weight with broad confidence limits, but nonetheless, it seems to be similar across the different groups of eGFR; a reduction in systolic blood pressure, which seems, again, consistent; and a DKA risk, at least from within the data provided by the sponsor, that has broad confidence limits but is not clearly different from that across the entire development program.

So my question to the FDA, specifically, is since we're worried about patients with type 1 diabetes who are at increased risk for a variety of adverse outcomes -- cardiovascular and renal among them -- why would we exclude a group of patients who could potentially benefit from this drug from the label? And in particular, because we know, as we just heard, that many of the potential benefits are not glycemic in etiology, or at least in their pathophysiology.

DR. ARCHDEACON: Yes. So I think when we

get to the questions, you'll see that we actually do ask you to consider all these factors for all the populations. I think all we're pointing out is one consideration that you might want to take into account is that the magnitude of A1C reduction appears to be somewhat lower in the less than 60, and there appears to be somewhat more uncertainty. We're not making any conclusions on your behalf about what that -- we're looking to you to put all of the pieces of this together for us, for each of these KDIGO categories.

DR. EVERETT: Thank you.

DR. LOW WANG: Dr. Irony?

DR. IRONY: Thank you. Ilan Irony. So my question is from the FDA briefing book, a discussion about the PK of sotagliflozin and exposure, a higher AUC in patients with eGFR less than 60 to 90 or less than 60 being 1.7, maybe 2 times higher than exposure in patients with normal eGFR, and the consideration for lower doses.

I'm not sure if this is a question for the applicant or for FDA, but if lower doses than 200

would be equally beneficial in terms of glycemic benefits but perhaps more favorable in terms of DKA? So that's one of my questions. It's a speculation because we have no data, but I just wanted to see.

DR. PENZENSTADLER: Right. The question is do we have any data or any information to suggest that a lower dose might be more effective, or similarly effective, for glycemic control but have a lower DKA risk? I guess I'll ask, first, our Office of Clinical Pharmacology colleagues to chime in, and I might have something additional to add.

DR. GUO: Dong Guo from Office of Clinical Pharmacology. As you mentioned, the PK, we have analyzed the dose normalized PK, is lower. And in the original submission, in overall population, the exposure efficacy response for the A1C, the relationship is relatively flat within the dose range, and the exposure response for the safety, we have found that exposure increased the DKA risk. I hope I answered your question.

DR. IRONY: Yes, you did, but that's the

reason for my consideration for maybe a lower dose would be the optimum in terms of balancing glycemic benefits versus glycemic risks in terms of DKA.

I have another comment. Again, I'm not considering SCORED or SOLOIST in the non-glycemic benefits, just considering the balance of benefits and risks only in terms of glycemia and the consequence of reducing the insulin dose. In a back-of-the-envelope calculation, this 20 percent reduction in level 2 hypoglycemia, for me, results in a number needed to treat of about 33 in the population of 60 to 90, and more or less the same in the population that the applicant originally proposed of 60 to 90 with albuminuria, or 45 to 90 without necessarily hypoalbuminuria.

So the question for me is, how do we balance something that now approaches the same level of numbers needed to treat and numbers needed to harm in DKA, in consideration of benefits and risks in terms of only looking at glycemia, not looking at cardiovascular disease or benefits, a reduction of A1C? The previous discussions are very valid, but

I'm trying to focus only on the short-term risks. The short-term risks of treatment of type 1 diabetes are hypoglycemia and DKA, excess or absence of insulin.

DR. PENZENSTADLER: Thank you for the question, Dr. Irony. Regarding the short-term risks, I think your back-of-the-napkin calculation that you just mentioned for hypoglycemia in the group of less than 60, number needed the treat of about 30 or so on, I think there are a couple issues about inferring absolute benefits from the hypoglycemia data.

First, this was SMBG. The data that we presented today was based on SMBG, confirmed events, and based on the data, it appears about somewhere between, I think, 14 to 18 events per year per patient. That seems rather low for a meter-validated blood glucose less than 55. So we're having a hard time here thinking about absolute benefits. That's really one issue there. And then the meaningfulness of less than 54, a lot of patients don't even pick up on it. I don't want

to broadly generalize, but it may or may not be symptomatic. That wasn't one of the criteria that we used in that endpoint.

So we really look to the panel to help us interpret what a 20 percent reduction in level 2 hypoglycemia might mean, and I guess I just wanted the panel to consider that it is challenging converting that to an absolute benefit.

DR. ARCHDEACON: Yes. I think what we would probably stipulate is -- and maybe Mr. Tibbits can help us -- my view is that almost every patient with type 1 diabetes is having many, many level 2 events through a year. So you have a 20 percent reduction, the number needed to treat is 1, and the the only question is how many of these events did they avoid. So all we're saying is avoiding one of those events, it doesn't seem worth going to the hospital with DKA, so how many of those do you have to avoid to be worth that? And that's the part that's a little bit hard, and we're just pointing out that we don't exactly know. If we had CGM data, we might be able to make a better estimate at

how many total level 2 events we were avoiding, and it's almost certainly more than one in everybody.

DR. LOW WANG: Okay. The last question from the panel before the lunch break.

Dr. Chrischilles?

DR. CHRISCHILLES: Betsy Chrischilles. It's actually a fairly minor point at this point because we've been talking about the Sentinel data, but I still do want to make it. I appreciate the hesitance to compare the claims data estimates with the trial data and the difficulty with calculating a number needed to harm; however, it would seem to me that we could at least look at the absolute risk of diabetic ketoacidosis in the claims data, as well as perhaps other real-world data where we've seen off-label use of SGLT2 inhibitors.

Has the FDA considered those data in light of the comparable absolute risk of DKA in the trial data? I noticed, for instance, the Sentinel data, the average follow-up time is about 3 months on drug, which is somewhat close to the trial time, which is more half a year. So anyway, could you

comment on that, the sort of real-world evidence, how your evidence fits with the trial data? It seems like those rates are somewhat comparable to me.

DR. PENZENSTADLER: Sure. Thanks for the question. For the first part, from the epidemiology perspective, I'll ask Dr. Po-Yin Chang to discuss the rates, and then I might have a few things to say about comparing that to the clinical trial data.

DR. LOW WANG: Dr. Yanoff?

DR. YANOFF: While we're getting our expert up, would you mind just clarifying what the intent of that analysis would be? Because we have looked at that data, but in different ways, and I'm not sure which one you're interested in. We haven't looked at trying to look at real-world data to see if the DKA risk would be higher in patients with type 1 using these drugs because we already know it is from the clinical trial data. At some point, we were looking at whether we could see trends.

So assuming it's true and assuming the

claims data are the same data over time, whether year to year we could see any decline in the rates of DKA, that is something we've done, and I believe is in our materials. But I think it will be helpful to understand what question you're trying to answer.

DR. CHRISCHILLES: Sure. I'm really most interested in just the rates of DKA, the type 1 diabetic population estimated from different real-world data sources, not specific to level of eGFR because I think comparing that with the type 1 diabetes trial population is just instructive.

DR. CHANG: Po-Yin Chang, Division of Epidemiology. In terms of the risk of DKA in type 1 diabetes population across CKD stage, we have done literature search on that, and there is only one publication, which is FinnDiane. The second piece is the sponsor's submitted T1D exchange data, and that's why we are also looking at the data in Sentinel query.

In terms of the absolute risk of DKA in type 1 diabetes population, we can look at the

absolute risk that's given, but the interpretation is tricky because if you don't have comparator groups for that absolute risk, it's hard to extrapolate or interpret the results. For example, the baseline characteristic could be different; it depends on different populations. So that's why we're still looking at the Sentinel analysis, trying to tease out whether there's an increased risk of DKA in type 1 diabetes with CKD.

DR. ARCHDEACON: This is Patrick Archdeacon, and I'll state out front that I'm not an epidemiologist. I think one thing that I found interesting was the overall incidence rates in the T1D exchange analysis were significantly lower than in the Sentinel analysis. I do have to wonder why is that, and maybe it's an ascertainment issue. I think, though, that we're reasonably confident in the ascertainment algorithms to identify someone who's hospitalized with DKA, so I'm not sure it's that.

I think it may just be the types of populations that are being captured. So perhaps

people who participate in the T1D exchange are not exactly representative of everybody who is in the healthcare system. I know Dr. Everett was interested in did we do propensity score matching, and I do think that would be interesting. If we did, that would tell us whether or not CKD was causing DKA, but what we get from the raw data, I think, is some insight into is there an association.

So when I see that people with more advanced CKD are experiencing DKA more often, it just makes me wonder, well, what causes people to have CKD? And maybe it's that you have poor glycemic control for many, many years. And what causes DKA? Having poor glycemic control. So perhaps, for whatever reason, someone has challenges being adherent to their insulin regimen. Well, they're going to develop CKD, and somebody who has challenges being adherent to their insulin regimen may be more likely to experience DKA.

Anyway, what I'm suggesting is I think the Sentinel probably does a pretty good job of

capturing a wide range of people, perhaps somewhat different than what the T1D exchange captured.

DR. CHRISCHILLES: Thanks.

DR. LOW WANG: Alright. We'll now break for lunch. Thanks, everyone. We'll reconvene again in this room at 1:15 Eastern Time. Please take any personal belongings you may want with you at this time. Panel members, please remember that there should be no discussion of the meeting topic during the lunch break amongst yourselves or with any member of the audience. Additionally, panel members, please plan to reconvene at around 1:05 p.m. to ensure that you're seated before we reconvene at 1:15. Thanks.

(Whereupon, at 12:37 p.m., a lunch recess was taken, and meeting resumed at 1:15 p.m.)

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

(1:15 p.m.)

Open Public Hearing

DR. LOW WANG: It's 1:15, so we will now begin 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 is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant. For example, the 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.

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for

your cooperation.

Speaker number 1, please state your name and any organization you are representing for the record. You have 3 minutes.

DR. ZELDES: Good afternoon. My name is Nina Zeldes. I am a health researcher of Public Citizen's Health Research Group. We have no financial conflicts of interest. Public Citizen opposes approval of sotagliflozin as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes and chronic kidney disease because there's a lack of substantial evidence demonstrating the effectiveness and safety of sotagliflozin in this population.

We are concerned that this application is based almost exclusively on post hoc analyses. These include the post hoc analyses of the TANDEM clinical trials. These trials were conducted for the initial application for approval of sotagliflozin for all adults with type 1 diabetes. The FDA rejected this application because the modest benefits of the drug did not outweigh the

unacceptable 8-fold increased risk of life-threatening DKA relative to placebo. Importantly, only about 8.5 percent of subjects in the TANDEM trials even fit the definition of type 1 diabetes and CKD in the revised population.

The application also includes a post hoc analysis of a trial conducted in adults with type 2 diabetes that was also not designed to assess glycemic control. No additional studies were conducted to assess the benefit and magnitude of harm of sotagliflozin.

The sponsor seems to have based its decision to limit the population on the assumptions that, quote, "similar improvements in glycemic control confer greater benefits to patients with type 1 diabetes and CKD," end quote, and that, quote, "the estimates of DKA risk in the overall TANDEM population are transportable to the revised population of patients" end quote; however, the available data do not substantiate these claims.

For example, we agree with the FDA that although the post hoc analysis, quote, "do not

support definitive conclusions about the magnitude of treatment effect," end quote, it appears that the treatment effect on A1C was smaller for some CKD patients than the treatment effect observed in the overall population. Except for potential risk reduction in hypoglycemia, no additional benefits were convincingly demonstrated.

More concerningly, the risk of DKA in the revised population appears to be similar or possibly even higher than in the overall population, although, again, due to the small number of observed events in the revised population, no meaningful conclusion can be drawn. Moreover, not enough is known about the potential effects of sotagliflozin on the DKA risk in CKD patients.

We therefore urge the advisory committee to vote no on the voting question and strongly recommend that the FDA not approve sotagliflozin for type 1 diabetes patients with chronic kidney disease. Thank you for your time.

DR. LOW WANG: Thank you.

Speaker number 2, please state your name and any organization you are representing for the record. You have 3 minutes.

MS. NORTON: Good afternoon. My name is Anna Norton, and I'm a person living with type 1 diabetes. I have received travel support from Lexicon to be here today, but I'm not being compensated for my time. Further, I do not have any financial interest in Lexicon or its competitors.

Thirty-one years ago, after being diagnosed with type 1 diabetes, my only choice for treatment was insulin. I injected it for many years until I chose to alter my management plan to incorporate an insulin pump, and later introduced other novel technologies such as continuous glucose monitor into my management for better quality of life. Along with my medical team, I have succeeded and seen little or no progression in the complications as a result of my career-long relationship with diabetes; however, I know the risk of long-term diabetes and the damage it can cause to my

cardiovascular and renal systems, especially as a woman nearing the age of 50; yet, insulin alone does not offer any protection to these organs.

Currently, there are no approved therapies available to myself as a person living with type 1 diabetes, and I know I need these protections just as people living with type 2 diabetes are afforded them. I understand the risks of DKA associated with the therapy discussed today; yet, with proper education with my healthcare team, I'm prepared to tackle that challenge just as I have learned to balance injecting insulin over the last 31 years, a hormone that if I take too much, can cause hypoglycemia, and if I take too little, can put me into DKA.

I have been lucky over the last three decades to have the support of a healthcare team and the diabetes community, but many others do not have that advantage, the access, or the education. Today, I urge you to afford me and others the option of additional therapy choices to continue to live with the best outcomes so we can continue to

be contributive members of society, as well as spouses, parents, employees, advocates, and friends. Thank you for your consideration.

DR. LOW WANG: Thank you.

Speaker number 3, please state your name and any organization you are representing for the record. You have 3 minutes.

MR. HANNAFORD: I'm Donald Hannaford. I'm a private citizen. I have consulted with biopharma companies over the years, including the sponsor. I am being reimbursed for my travel expenses but not for my time. I'm making this statement as a type 1 diabetic for 44 years. I'm a little unusual in that I was diagnosed my senior year in college. It was a life-altering experience because at that point, I had accepted a commission in the U.S. Army and expected to wear olive drab for 35 years. They don't like needles.

At the same time, I was very fortunate to have been diagnosed at the dawn of a new era in diabetes treatment. My first insulin was pork and beef derived. A year later, recombinant human DNA

insulin came on the market, and all the advances that have come since then, including pen injector devices, the changes in insulin. Today, I use an integrated pump and CGM, but there have been few therapies that have been introduced. Most of them have been for type 2.

I appreciate all of these advances, and I also appreciate this committee's consideration of a new therapy for type 1s; type 1s are largely overlooked. My perspective as a type 1 is that staying in range is your biggest challenge. We've been told for years and years and years that it's staying in range that makes it possible for us to forestall the complications down the line, and that's something that we have to deal with every single day. There is no escaping it. And because of that, I think that we need to increase the number of things in our armamentarium for type 1 diabetes.

My point is that type 1s are used to weighing costs and benefits every day. Staying in range means largely avoiding hypoglycemia. I have

had many, many hypoglycemic events, some very severe, and for those who don't think that it's important to trade that off, be lucky you're not a type 1 diabetic. So I hope that you will consider sotagliflozin for the adjunct therapy for glycemic control in CKD. Thank you.

DR. LOW WANG: Thank you.

Speaker number 4, please state your name and any organization you are representing for the record. You have 3 minutes.

DR. BUSCH: Hi. My name is Robert Busch. I'm Director of Research at Albany Medical Center Endocrine Group, and I'm representing myself, 15 fellow endocrinologists, and my patients. I have no conflict of interest. We were in the SCORED trial with sotagliflozin, and we were in the TANDEM trial in type 1 patients. We were in both of those studies.

As the other previous two patients just said, patients with type 1 diabetes haven't had the benefit like what patients with type 2 have with GLPs and SGLT2s, preventing macrovascular disease

and renal disease. Type 1 patients can take insulin. Over the last 100 years, we've still had insulin, different ways to deliver it so they can get glucose better, but they have not had the benefit of other drugs that could lower renal disease or macrovascular disease.

Based on what has been shown with SGLT2s showing tremendous renal benefit and cardiac benefit, I would implore the FDA to consider approving sotagliflozin. The studies were very impressive in terms of not only A1C lowering and getting people in range, as speaker 3 said, but lowering kidney disease, as speaker 2 is very concerned of that, as we are. Other than giving an ACE, or an ARB, and good control, there's nothing else we could do with type 1. There's plenty we could do with the pillars of therapy for renal protection in type 2, but the frustration is treating type 1. Sotagliflozin would offer these additional benefits to the patient, not only for renal benefit and potential cardiac benefits, but also better time in range.

In terms of the DKA risk, which we always worry about risk versus benefit, patients with type 1 very often have urine ketone strips home, and during the visits can have beta hydroxybutyrate as we did in the studies. So I feel the risk of DKA can be mitigated against by educating the patient: no food, no drinks, no sotagliflozin. Check your urine ketones. They could mitigate against that risk; yet, still have the significant benefit that type 2s have all the time with either GLPs or SGLT2s. And now we finally have a drug that can hopefully lower their risk of kidney disease, heart failure, macrovascular disease, and still mitigate against the DKA with appropriate measures in the appropriate type 1 patient.

Thank you very much for the time, and I'm speaking on behalf of my patients and my partners, my 15 partners who treat a lot of patients with type 1. Thank you.

DR. LOW WANG: Thank you.

Speaker number 5, please state your name and any organization you are representing for the

record. You have 3 minutes.

DR. DUTTA: Good afternoon. My name is Dr. Sanjoy Dutta. I'm the Chief Scientific Officer at Breakthrough T1D, formerly JDRF, the leading global type 1 diabetes research and advocacy organization. Breakthrough T1D has co-funded several clinical trials of sotagliflozin in T1D. The grant terms of some studies include the potential for Breakthrough T1D to receive a portion of the net royalties to fund further research.

Some people believe improvements in diabetes care have progressed such that little risk should be tolerated when considering new therapies for T1D. We disagree. Insulin is not a cure, and the physical, cognitive, and emotional burden of managing T1D with insulin are still not adequately recognized. Recent data has shown, and many people presented today, only 26 percent of individuals with T1D in the United States are able to achieve the recommended hemoglobin A1C target of less than 7 percent, and people with T1D still die 11 years earlier than their non-diabetic counterparts.

Novel therapies that improve glycemic control, clinical outcomes, and quality of life for those with T1D are desperately needed, especially for those who also live with chronic kidney disease. The evidence shows that the addition of sotagliflozin results in improved A1C, as well as reduced hypoglycemia and increased time in range, both glycemic outcomes that are well established as important and clinically meaningful to clinicians and most importantly patients.

It is also reasonable to expect the renal benefits of sotagliflozin seen in people with type 2 diabetes and chronic kidney disease would be seen in T1D, and we are encouraged by the data demonstrating sotagliflozin's benefits on markers of kidney function in T1D.

While therapies like sotagliflozin are increasingly available for individuals with type 2 diabetes, CKD, et cetera, people with T1D are being left behind and are consistently excluded from studies. Breakthrough T1D strongly believes in the potential of sotagliflozin as an adjunctive to

insulin, especially for those with CKD, and continues to support research studies to this end with several ongoing studies.

As we have heard today, a key consideration for the safe use of sotagliflozin is the risk of DKA. DKA is a concern for all individuals with T1D, and vigilance of DKA is a routine aspect of living with T1D, regardless of the use of sotagliflozin. DKA risk has been shown to increase with the use of SGLT inhibitors, and this requires appropriate monitoring and mitigation strategies. Experts have convened to consider this risk, and an international consensus has been published with agreed-upon strategies to mitigate the risks of DKA for individuals with T1D using SGLT inhibitors.

We ask the FDA and the committee to carefully consider the risks of living with T1D today, even with the best available care with devices and insulins, as they consider if the benefits of sotagliflozin still outweigh the risks in those with T1D and CKD. Thank you for your time.

DR. LOW WANG: Thank you.

Speaker number 6, please state your name and any organization you are representing for the record. You have 3 minutes.

DR. RODBARD: Yes. Good afternoon. I'm Dr. Helena Rodbard and here speaking as an individual. I have no conflicts of interest, and I'm not being compensated for my testimony, travel, or any other expenses.

I'm an endocrinologist in the Washington, DC area in clinical practice for the past 42 years. I have cared for thousands of patients with type 1 and type 2 diabetes. I have also conducted a program of clinical research for the management of people with diabetes for the past 25 years, including more than 150 clinical trials for many of the therapeutic agents currently FDA approved for either people with type 1 or type 2 diabetes. These clinical trials have been sponsored by the pharmaceutical industry.

I've been actively involved in many clinical organizations, including the American Association

of Clinical Endocrinologists, of which I was a founding member and former president. I've been involved with the Endocrine Society; the American Diabetes Association; the European Association for the Study of Diabetes; among others. I've also been involved in the development of guidelines for the management of people with diabetes and several other metabolic and endocrine disorders.

At present, there are very few therapeutic options for people with type 1 diabetes. The currently available therapy is limited to insulin, and as wonderful and life saving as insulin is, it is frequently associated with increased risk of hypoglycemia and weight gain. I've had the opportunity to be the principal investigator in clinical trials using SGLT2 inhibitors and sotagliflozin in people with type 1 diabetes.

Over the past several years, I have prescribed off-label SGLT2 inhibitors with very favorable results, and I have to say I never had a case of DKA in my practice. Specifically, they have seen improvements in hemoglobin A1C levels,

reduced glycemic variability, and the patients reported improved quality of life, which is absolutely essential.

Sotagliflozin and drugs of the SGLT2 class have many beneficial effects in people with type 1 diabetes, including reduced risk of hypoglycemia; reduced levels of main glucose; reduced time in range; increased time in range and reduced glucose levels above range; reduced glycemic variability; reduced body weight, as well. Potential risk of ketosis or ketoacidosis can be mitigated by adherence to recommendations from expert panel consensus, and guidelines have been published to that effect. Thank you very much for your attention. I appreciate the opportunity.

DR. LOW WANG: Thank you.

Speaker number 7, please state your name and any organization you are representing for the record. You have 3 minutes.

DR. LAPUERTA: I'm Pablo Lapuerta. I have some slides. I'd like to disclose that I used to work at Lexicon Pharmaceuticals and still have

equity ownership in it. I also have equity ownership in Yanjing Therapeutics, which is developing a SGLT inhibitor with special promise in type 1 diabetes.

Five years ago, this committee was presented an original benefit-risk projection of sotagliflozin. It included extrapolation of the benefits in A1C affecting complications of diabetes, the reductions in blood pressure and body weight affecting cardiovascular disease, and it included the observed reduction in severe hypoglycemia at one year and the increase in DKA at one year.

It was a positive profile. There was discussion of extrapolation. There was also a discussion of caring for patients, and committee members involved in the direct care of patients with type 1 diabetes voted for approval. Their votes have been supported by numerous publications of the original clinical trial results and meta-analysis, indicating that sotagliflozin can reduce cardiovascular disease, renal disease, and

hypoglycemia.

Now, another very important thing happened in the last five years. In the last five years, approximately 100,000 people living with type 1 diabetes in the United States have died. This is relevant to the benefit-risk consideration because what are the causes of death? The most common cause of death is cardiovascular disease. There's a question, how do you weight cardiovascular disease against DKA? The answer is you weight it very strongly because it's the most common cause of death. Other common causes of death in the last five years of these 100,000 patients have included renal disease and hypoglycemia.

There's a discussion about extrapolation, again, at this meeting. One of the things to consider is the position of the cardiorenal division. The cardiorenal division extrapolates the benefits of reducing systolic blood pressure, and has specifically stated that a 3 millimeter reduction in systolic blood pressure is appropriate for labeling because it's a reduction in

cardiovascular disease risk.

So I hope there's a good discussion today of the committee; that it addresses the urgency in getting new treatments approved for type 1 diabetes, it weighs the most important causes of death, and that it supports the approval of sotagliflozin. Thank you.

DR. LOW WANG: Thank you.

Speaker number 8, please state your name and any organization you are representing for the record. You have 3 minutes.

MS. APRIGLIANO: My name is Christel Marchand Aprigliano, and while I received travel support from Lexicon to be here today, my words, opinions, and experiences are my own. I was diagnosed with type 1 diabetes in 1983, and I quickly learned about all of the risks living with this relentless disease and the risk of living less of my life because of the complications. Frankly, back then, I thought I'd be cured by now. Instead, I've come to view my body as a ticking time bomb, wondering when and how the damage of 41 years of

living with type 1 diabetes will manifest.

I ride a fine line, as everyone living with type 1 diabetes does, self-managing a disease where the only widely drug available to us is insulin. Take too much, immediate risk for severe hypoglycemia, which, by the way, is terrifying and deadly. Take it from personal experience. Take too little, risk of diabetic ketoacidosis and long-term complications, and that line never goes away.

For those with type 1 diabetes diagnosed with chronic kidney disease, keeping glucose levels in range has been shown to delay progression to end-stage renal disease, which is currently -- thanks to the last speaker -- the leading cause of death for individuals in the mid-years of type 1 diabetes duration. Insulin keeps us alive, but it does nothing to help to protect us from complications.

SGLT2 inhibitors do keeps glucose levels in range and provides cardio protective, as well as renal protective benefits. We recognize that they

provide both, and there are risks. We recognize the risk of EDKA as elevated when taking SGLT2s as a type 1. We recognize risk. We live with risk every day, and reducing the risk of EDKA will require provider and patient education, as well as home-based blood ketone testing.

The type 1 community is already adept at mitigating risk. We carry glucagon, and rapid glucose, and extra supplies, and we wear CGMs, and we work with medical professionals to keep our glucose levels in range. I'm grateful for insulin, it keeps me alive, but it's not enough. The benefits of sotagliflozin outweigh the risks, and we need additional treatments to increase in-range glycemic management for those of us at greatest risk of premature death due to type 1-induced chronic kidney disease.

I hope that you'll recommend the approval for those who need it most today, and for those like me who will need it in the near future. Thank you.

DR. LOW WANG: Thank you.

Speaker number 9, please state your name and any organization you are representing for the record. You have 3 minutes.

DR. ROSAS: My name is Sylvia Rosas. I'm not being compensated for my testimony. I'm here on behalf of the National Kidney Foundation and Patients with Kidney Disease. NKF, now in its 75th year, is the largest, most comprehensive, long-standing, patient-centric organization dedicated to the awareness, prevention, and treatment of kidney disease in the United States. In addition to being the immediate past president of the NKF, I'm also a nephrologist and a clinical trialist at the Joslin Diabetes Center, caring for patients with diabetes and kidney disease. I'm an investigator for the Sugar and Salt study that is being sponsored by Breakthrough T1D with medications provided by Lexicon.

It is estimated that one-third of individuals with type 1 diabetes develop kidney disease during their lifetime. In contrast to the three seminal medications that now are available

for patients with type 2 diabetic kidney disease, in the last three decades, there has not been a novel therapy intervention to mitigate kidney disease in individuals living with type 1 diabetes. Strict glycemic control has been shown to decrease the damage to the small vessels that lead to kidney failure; however, the vast majority of patients with type 1 diabetes do not need the glycemic targets, and therefore, therapeutics and innovation in this area are needed.

In order to avoid CKD progression to kidney failure, early intervention is necessary. Preservation of kidney function is the goal that can only be achieved if we're able to identify early so that patients can benefit from treatment options; however, only 40 percent of individuals with diabetes are screened for chronic kidney disease annually, and since CKD is often asymptomatic, screening for diagnosis is essential; however, the lack of additional therapeutics for treatment of kidney disease in type 1 diabetes is commonly cited as a reason not to screen for kidney

disease, as there is nothing to be done.

We acknowledge the possible risk of diabetic ketoacidosis in patients. This mortality risk is currently estimated at 0.4 percent a year in the U.S., however, the mortality of an individual on dialysis is above 20 percent a year. This is higher than most common cancers, including breast and prostate; therefore, high-risk individuals for kidney failure, such as those with a GFR of 45 to 60, or those with a GFR greater than 60 with albuminuria, could benefit from improved glycemic control and the cardiorenal protection from an SGLT1-2 inhibitor.

Patients with chronic kidney disease and diabetes should be educated on mitigation strategies for DKA. The NKF supports increasing therapeutic options for individuals living with type 1 diabetes and chronic kidney disease, and accordingly, we're ready to continue to support education of both patients and healthcare providers. We're cautiously optimistic about the positive impact of this medication on kidney

failure trajectory that will require additional studies. Thank you for the opportunity to participate in this session.

DR. LOW WANG: Thank you.

Now, we'll actually skip over to speaker number 11 because 10 is not available. So speaker number 11, please state your name and any organization you are representing for the record. You have 3 minutes.

DR. RICE: Good afternoon. My name's Donna Rice. I have no financial disclosures. I am the Chief Operating Officer for DiabetesSisters, a national nonprofit organization dedicated to improving the health and quality of life for women living with diabetes. I am also a nurse and a certified diabetes care and education specialist. With my professional background and a deep understanding of the challenges faced by women with type 1 diabetes, I am here today to share how DiabetesSisters supports these women through education and empowerment, particularly as they consider new therapies like sotagliflozin as an

adjunctive therapy treatment to insulin.

Managing type 1 diabetes is a daily challenge. While insulin therapy remains the foundation of treatment, many women still struggle to maintain optimal blood glucose management. This drug offers a promising option for improving A1Cs, supporting weight management, and enhancing cardiovascular and kidney health, which are key benefits for women faced with increased risk of complications.

At DiabetesSisters, we regularly hear from our members who express frustration with the limitations of existing treatments. They are eager for new treatment options that offer better control and offer the potential of mitigating some of the long-term complications. Women are seeking options and choices. Sotagliflozin offers this potential, and we encourage the committee to consider the positive impact this drug could have on thousands of women who are managing the complexities of type 1 diabetes.

As a healthcare professional, I do

understand the importance of balancing the benefits with safety, particularly when it comes to mitigating diabetic ketoacidosis. At DiabetesSisters, we are committed to ensuring that women in our community have access to expert education and the support they need to manage these risks effectively.

To our comprehensive education platform, which reaches over 30,000 women, we provide practical tools and resources on safe diabetes management. Additionally, our 20 virtual meet-ups per month offer a space for women who share experiences and gain confidence in monitoring blood glucose and ketone levels, recognizing the early signs of DKA, and adjusting insulin therapy when necessary.

While we emphasize the importance of educating women on the benefits and risks of therapies, we encourage the committee to consider its potential role in addressing the unmet needs in type 1 diabetes care. With proper guidance, education, and monitoring, we are confident that

this drug will offer substantial benefit to women who have long awaited additional treatment options. Thank you for your time and considering the needs for women living with type 1 and type 2 diabetes.

DR. LOW WANG: Thank you.

Speaker number 12, please state your name and any organization you are representing for the record. You have 3 minutes.

MR. BRYANT: My name is Chris Bryant, and I'm a private individual. The sponsor is reimbursing my travel, so I can be here today, but I'm not being reimbursed for my time. I'm here to talk about my journey of living with type 1 diabetes along with CKD or chronic kidney disease. I had type 1 diabetes for a very long time, as I was diagnosed when I was 16.

At any age that you're diagnosed with this chronic illness can be challenging, but I believe that it is particularly challenging when you are of adolescent age. At that age, most are going through social development, being academically developed, as well as living with the notion of

invincibility. You're not thinking of being diagnosed with a chronic illness until I was. Being diagnosed as a type 1 diabetic is simply overwhelming. The common emotions of anxiety and depression are prevalent. The cases of hypoglycemia and hyperglycemic are nothing short of fearful. These emotions of fear grow as the notion, if you do your best and your best is not good enough, then you will suffer from the consequences or complications stemming from diabetes. Several years later, I was diagnosed with late-stage CKD. Apparently, my best wasn't good enough.

Diabetes is a 24-hour illness, as it is a constant struggle of trying to maintain it. Being diagnosed with a CKD in a late stage caused me to crash into dialysis for a short period of time. Fortunately, I had a kidney transplant from an altruistic donor. She saved my life, and I am grateful to her and her family for what they've done for me and my family.

A year later, I was fortunate to receive

another transplant, a pancreatic transplant. It was the first time in my adult life that I got a chance to experience what it was like to not have diabetes. It was the best feeling. After three years, the pancreas rejected because I came down with a terrible virus. Eight years later, the kidney rejected as well, and then I was back on dialysis.

I thought about getting another kidney transplant and had a discussion with my greatest supporter, my wife. We discussed the risks and benefits of going through the process again. In any health situation, there is a risk and a benefit. The risk was going through another major surgery. Another was the notion of being immunosuppressed, raising my risk of contracting a virus or an illness, including cancer; however, the benefit was the notion of getting back the quality of my life that I lost. We decided to have another transplant. It's now been six years since I've been transplanted.

Frankly speaking, diabetes has come a long

way over the last three decades. I'm currently wearing an insulin pump along with a CGM. It's a game changer, but there is more to be done, and more options and medications need to help manage blood glucose, imperative, to avoid complications that I've experienced. I hope that today, the pharmaceutical companies such as Lexicon can continue to help those like me control my sugars to avoid any further complications. Thank you for your time.

DR. LOW WANG: Thank you.

Speaker number 13, please state your name and any organization you are representing for the record. You have 3 minutes.

MS. HEVERLY: Good afternoon. I'm Julie Heverly from the diaTribe Foundation, a nonprofit dedicated to ensuring that people with diabetes have the resources needed to thrive. I have not received any support related to my remarks. diaTribe does receive funding from Lexicon, other pharmaceutical companies, and supporters of our mission. Today's remarks and those that we

submitted are those of diaTribe's alone.

For over a quarter of a century since my diagnosis with type 1 diabetes, I have benefited from diabetes innovations, but despite my intentional nutrition plan, daily exercise, education, and access to insulin pumps and CGMS, my diabetes remains unpredictable and frustrating. And I'm not alone. You've heard today that less than 30 percent of us have an A1C below the target of 7. With insulin and tech, my A1C was above 7 until my endocrinologist prescribed an adjunctive therapy. Using it reduced my insulin resistance, flattened out my glucose levels, lowered my A1Cs consistently below 7 for the past 4 years.

Despite the improvements to my health and quality of life, because these medications are not approved for type 1 diabetes management, and therefore are not reimbursed, access has been cost prohibitive and oftentimes impossible for me and many others with type 1 to obtain.

People living with both type 1 and CKD face additional challenges. CKD makes it harder to

manage type 1, but tight glucose control is essential to slow CKD's progression. The use of sotagliflozin in type 1 has been found to increase glucose stability, reduce A1C and insulin needs, improve weight and blood pressure, and provide protection benefits, increasing treatment satisfaction and reducing diabetes distress. That is a compelling argument for benefits significantly outweighing risks.

Diabetes is an insidious, progressive condition. More therapeutic flexibility is needed. People with type 1 uniquely understand medication risks and weigh them daily. Those with type 1 and CKD are aware additional treatments carry risk, but they are also acutely aware of the risk associated with their CKD advancing.

Treatment options are needed for the best balance of these risks so individual care can be leveraged. CGM use in this population can facilitate effective diabetes management, identify elevated glucose quickly, and largely avoid severe cases of DKA. We encourage the development of a

combined ketone and glucose monitor, but while we're waiting for that, patient organizations like diaTribe continue to educate about the recognizable signs of DKA, when to test, and how ketone monitoring should be standard risk management protocol for all of us.

We urge the FDA to also recognize the additional benefits of CGM metrics like time in range for improving health outcomes and the quality of life for individuals living with diabetes. The voice of people with diabetes must be considered when discussing these advancements in therapies that directly affect our lives. As one of those people, I thank you so much for this opportunity to share my view that the approval of sotagliflozin will give people with type 1 and CKD a valuable new treatment option.

DR. LOW WANG: Speaker number 14, please state your name and any organization you are representing for the record. You have 3 minutes.

DR. MENDE: Good afternoon. I'm Christian W. Mende, MD. I'm a nephrologist and

Clinical Professor of Medicine at the University of California in San Diego. I have no conflict of interest pertaining to sotagliflozin; however, I have treated many, many patients with in situ inhibitors, almost all of them type 2 because of the approval issues.

I'd like to point out that type 1 diabetics have an over 40 percent risk of developing CKD, and with this, a very high risk of CKD progression to end-stage kidney disease, needing dialysis or transplantation, and have a very high risk for cardiovascular disease, as well as heart failure. So the only drugs available to me, FDA approved for CKD in type 1 diabetics, are ACE inhibitors and ARBs.

We have not had, for about 25 years, any additional renal protective drugs approved for type 1 diabetics. They have essentially been excluded from all CKD trials, including prior trials with SGLT2 inhibitors, MRA, or GLP-1 receptor agonists. The SCORED trial of sotagliflozin on a secondary and additional

analysis clearly showed significant reduced renal and cardiovascular endpoints, especially in type 1 patients. It would be very helpful to reduce their albuminuria, their renal progression, and their high cardiovascular risk, including their high risk for heart failure.

Type 1 diabetics actually have been treated as a stepchild as far as being included in type 1 trials for diabetes, and they clearly deserve to have an SGLT2 inhibitor such as sotagliflozin available for the treatment in CKD and to reduce their associated risks, as I have stated before. In addition, SGLT2 inhibitors are already used off label anyway, as you have heard, by many endocrinologists, cardiologists, and nephrologists, but, unfortunately, only available to those patients who are financially in the position to pay for the drugs because of no official approval.

The care of our type 1 diabetics would be greatly improved with an approval of an SGLT2 inhibitor for CKD, and the patients would greatly benefit from a renal, as well as cardiovascular

standpoint. Thank you.

DR. LOW WANG: Thank you.

Speaker number 15, please state your name and any organization you are representing for the record. You have 3 minutes.

MS. CARNEY: My name is Brittany Carney, and I'm the Executive Director of Taking Control of Your Diabetes, or TCOYD, a not-for-profit organization founded in 1995 with a mission to bring education and motivation directly to the people living with diabetes so they can be empowered to become an active member of their healthcare team. TCOYD has received funding from a number of pharmaceutical companies, including Lexicon.

For the past 30 years, TCOYD has worked to disseminate information about the latest advancements in diabetes care directly to the diabetes community, receiving over 17 million views on our programming. Time and time again, our most watched programming is breaking news about recent device and medication approvals relating to the

complications of diabetes, including eye, kidney, nerve, and heart disease.

We have created several educational pieces about the benefits of oral diabetes medications, explaining the significant improvements for people with type 2 diabetes, and the number one question we've received over the past five years is how can type 1s get access to these life-changing medications? Our community is hungry for more options to improve their treatment plan, and more motivated than ever to achieve glycemic control.

I know that the majority of people with type 1 diabetes have an extremely difficult time getting their A1C and time in range to goal. Having a once-a-day oral medication to help improve these goals on top of insulin would be a tremendous benefit to the type 1 community. Additionally, with all of the education we do or run important tests to diagnose chronic kidney disease, such as the UACR and the eGFR, I'm shocked by how many type 1s in our community are dealing with CKD. Although the data on reducing the progression of

kidney disease with an SGLT inhibitor and type 1 diabetes is not extensive, I do believe, based on the concerns from our type 1 community, that sotagliflozin could be a huge benefit.

Of course, we know that education about these medications must be paired with education on the risks such as diabetic ketoacidosis. We have several programs on the causes, symptoms, and early treatments of DKA that our audience has participated in, and we'll continue to focus on this important message to make sure the full 360 degree view of this treatment plan is addressed. We are happy to share this program with the FDA, other not for profits, and those in the industry.

Patient advocacy organizations like TCOYD hear first-hand from our community they're struggling to meet their goals, and for many of them, it's not for lack of trying. Anything we can do to improve the lives of people living with diabetes through better control is a positive move in the right direction and could have a tremendous

impact on health outcomes overall as a country. With the right tools and resources, people living with diabetes can live a healthy, happy, and more productive life. Thank you for your time.

DR. LOW WANG: Thank you.

Speaker number 16, please state your name and any organization you are representing for the record. You have 3 minutes.

MS. CILENTI: Good afternoon. My name is Ginine Cilenti, and I'm here representing the Diabetes Foundation. We have no conflict of interest, and we're not being compensated for our time or expenses.

The Diabetes Foundation is 34 years old, and we are located in New Jersey, offering prevention and self-management support to New Jersey residents living with T1D and T2D. We provide access to care to ensure essential needs are met, including medication, education, A1C screenings, and social support. We work directly with patients, with providers, and with other community partners to deploy our services. We've provided over the years

tens of thousands of people and their families with help. As prevalence and incidence of T1D and T2D continue to rise, our services are continuing to increase as well.

I say this all as a way to explain why we are here today. We're a voice for men, women, and children struggling with diabetes. One common thread that we hear over and over, wherever we are, in our office or out in the community, is that people are experiencing overwhelming despair and desperation no matter what stage of progression of their disease. In particular, our participants with T1D are exhausted by the long road of living with the condition, particularly with the inconsistency in how their blood sugar levels are, regardless of how well they are managing their care.

When the DF was informed that there may be a new treatment for people with T1D living with chronic kidney disease, a resource to help with glycemic control, we recognized that this could be game changing for those we serve. I'd like to tell

you about a participant of ours. His name is Umberto. He engaged with us about two years ago. He was living with T1D blind and chronic kidney failure. His quality of life was limited. We provided him with education about disease management, and he attended our social support groups for about a year so that he could express how he was physically and emotionally feeling. My team member and colleague, Grace, mentored him. He passed away about a year after we began working with him, and his struggles were complex and devastating for all of us that knew him.

Today, I think of Umberto and the possibilities that a new treatment would have offered him. It could have enhanced his quality of life, it could have helped him to be more productive, and it could have very importantly given him the opportunity to feel good when he was with his family, his children, and his grandchildren. The public needs resources that can offer better health; that can offer hope. We believe that a new treatment that could have helped

him manage his blood sugar would have been beneficial to Umberto, and we know that it would be valuable for public health. Thank you for your time.

DR. LOW WANG: Thank you.

Speaker number 17, please state your name and any organization you are here to represent for the record. You have 3 minutes.

SPEAKER 17A: We represent Close Concerns, our healthcare information organization covering for those working in the field, scientific, regulatory, and advocacy gatherings in diabetes and obesity, as well as happenings in the fields across manufacturers, nonprofits, policymakers, and stakeholders. Our disclosures, we have no conflicts of interest, nor do we receive any funding or travel support to be here.

As we've heard today, treatments for type 1 diabetes are limited and falling short, particularly for those with complications. Achieving long-term optimal glycemic targets dramatically reduces the risk of complications in

T1D, but only a small fraction of adults with T1D achieve A1Cs under 7 percent. Among modifiable risk factors, glycemic management is paramount in reducing kidney disease progression. There is a huge opportunity here to reduce the risk and consequences of DKA.

SPEAKER 17B: Data published just last week in JAMA under prescription of GLP-1 receptor agonists and SGLT2 inhibitors in people with type 1 diabetes showed that off-label use of SGLT2 inhibitors for T1D has increased from one-tenth of 1 percent in 2013 to 2.4 percent in 2023.

SPEAKER 17C: To translate, that's an increase from 1400 people to 36,000 people with T1D who were taking SGLT2 inhibitors off label.

SPEAKER 17B: However, there is no guidance on the use of SGLT2 inhibitors in T1D. This fact was made clear by the renowned Dr. Leslie Eiland of the University of Nebraska in a comment she wrote last week on your very helpful FDA public docket. There are dozens and dozens more like it. Greater guidance and regulation on SGLT2 inhibitors for T1D

are much needed and would be greatly appreciated.

SPEAKER 17D: Even one person with an untreated euglycemic DKA is one too many. Adjusting insulin and keto monitoring aren't easy, but it is possible with FDA regulations. REMS protocols can be written, black boxes can be created, the STICH protocol can be mandated, and should be used. While DKA can be fatal, every kind of DKA, translational and euglycemic can be prevented, especially with proper oversight.

MS. CLOSE: So sometimes I feel like we're a little bit in the wild west. If we can go to the next slide for just a second -- I guess we didn't get our wild west picture in here -- imagine cowboys out there, all over the place. People are doing many different things. Some people are taking SGLTs because their blood glucose is going up and they don't know what to do. We love the idea of this being regulated so we can figure out how much less insulin could be taken and to figure out how to avoid euglycemic DKA. It is happening out there.

We believe that, as Julie said so eloquently, CGM in-range metrics have increased dramatically for people who have been lucky enough to be in trials. What we're asking you to do is please regulate this therapy. Simply stated, the current status quo is doing harm. You have the power to change that, and we so hope that you will.

DR. LOW WANG: Thank you.

Speaker number 18, please state your name and any organization you are here to represent for the record. You have 3 minutes.

DR. BERGENSTAL: Thank you very much. I'm Rich Bergenstal, the Executive Director of the International Diabetes Center in Minneapolis, and I'd like to outline where I think sotagliflozin fits in the ongoing transformations of the management of type 1 diabetes. I have no personal conflicts of interest, and very specifically, I have no disclosures regarding sotagliflozin, or Lexicon, or no sponsorship from them.

Everyone has probably seen this slide of the celebration of the 40th anniversary of DCCT EDIC.

I've annotated hit here a bit because now it shows not only that achieving an A1C of 7 reduces the risk of microvascular complications, but it shows that for 20 years after the DCCT, we have struggled to achieve optimal glycemic control because of hypoglycemia.

So this led to the introduction of CGM, which thankfully started to bend the curve and introduce the concepts of time in range and time below range, which are the two metrics we use to manage type 1 diabetes today. But that was not enough, so AID was introduced to further bend the curve towards better control, but you heard today that 50 percent of people only are on AID, and 20 to 30 percent achieving A1C less than 7, so we need adjunctive therapy that can further increase time in range and decrease time below range such as sotagliflozin.

I know the panel is data-driven, so I'll show you one slide that's about to be published from the T1D Exchange that says, in orange, "40 percent of people on AID today are not

achieving this time in range and time below range targets that are so important," and the right side of the side, I won't go over again, shows the PERL study just reinforcing that good glucose control in people with kidney disease can slow the progression.

I want to show you one bit of data, a survey we took for an application where we've submitted interviewing 20 of our endocrinologists, and we asked them, "Would you prescribe an SGLT2 inhibitor if FDA approved it?" And they said yes. Ninety percent would prescribe it for those with CKD in type 1 and 10 percent said CHF. And then I asked, "Well, how about the DKA? Is it manageable?" The answer was overwhelmingly yes.

There is a dramatic increase in our access to patients, remote access, since the pandemic. Please don't look back to 2019 data. We are in much closer contact with our patients today. We all have the STICH or we like the STOP protocol for managing sick-day illness and managing DKA. Our endocrinologists may be able to wait for the FDA,

but people with type 1 diabetes and CKD really can't wait much longer. We have a therapy that specifically addresses their needs, and I think the benefits far outweigh the real but manageable risks of DKA. Thank you very much for your attention.

DR. LOW WANG: Thank you.

Speaker number 19, please state your name and any organization you are here to represent for the record. You have 3 minutes.

DR. SHAH: My name is Dr. Nirali Shah. I'm an endocrinologist and Associate Professor in Medicine at the Icahn School of Medicine at Mount Sinai. Today, Dr. Janet McGill, Professor at the University of Washington, and I will be presenting on behalf of the American Association of Clinical Endocrinology. ACE is a global inclusive community of more than 5700 endocrine-focused clinical members, affiliates, and partners. We have no conflicts to disclose and are not being compensated for our time.

We want to highlight the current gaps and unmet needs in the management of type 1 diabetes.

Despite advances in diabetes technologies such as continuous glucose monitoring devices and insulin pumps, only 17 percent of youth and 21 percent of adults with diabetes achieve their target hemoglobin A1C. Type 1 diabetes reduces the life expectancy by an average of 11 to 13 years, with cardiovascular disease being the leading cause of death. Kidney function deterioration is a major complication of type 1 diabetes, leading to reduced quality and quantity of life. Challenges with insulin-only treatment options include hypoglycemia and weight gain associated with higher insulin doses.

The benefits of sotagliflozin for type 1 diabetes patients have been demonstrated through the inTandem clinical trial program, which examined the efficacy and safety of adding sotagliflozin to insulin therapy in type 1 diabetes patients. The results demonstrated a 0.21 to 0.32 percent reduction in hemoglobin A1C; 10 to 13 percent increased time in range; decreased weight 2.2 to 4.3 percent; 6 to 12 percent reduced insulin

doses when compared to placebo. Patients also reported higher treatment satisfaction and lower diabetes distress scales.

Sotagliflozin has shown improvements in key kidney function biomarkers in type 1 diabetes patients compared to placebo. It has also demonstrated cardiovascular renal benefits in patients with type 2 diabetes.

Next slide, please, and I will be handing it over to Dr. McGill.

DR. McGILL: So many of the expert groups who have presented here have outlined strategies to mitigate the risk of DKA. I want to bring to the committee's attention the fact that the data on DKA, with all of the adjunctive therapy trials using SGLT2 inhibitors or SGLT1-2 inhibitors in patients with type 1 diabetes, were done before widespread use of continuous glucose monitors; before widespread use of AID pumps; before remote patient monitoring; before many of the tools that we have today to enhance glucose control but also mitigate risks of therapies such as sotagliflozin.

Clearly, careful patient selection; 60 percent of persons with DKA have been in DKA in the past year, perhaps using lower doses shown in one set of trials; providing education; avoiding substantial insulin dose reductions; and using the STICH OR STOP DKA protocol. We promise to advocate for greater use of ketone meters, which are more sensitive than ketone strips, but not universally approved or covered by insurance.

In sum, we strongly recommend the approval of sotagliflozin for adjunctive treatment for type 1 diabetes who are facing chronic kidney disease and other devastating complications. We support risk mitigation strategies, and we'll work with --

DR. LOW WANG: I'm sorry. Could you start to wrap up?

DR. McGILL: Thanks.

DR. LOW WANG: Thank you.

Speaker number 20, please state your name and any organization you are here to represent for the record. You have 3 minutes.

DR. HERRERA: Hi. How's everybody? Distinguished members of the EMDAC, my name is Carolina Solis-Herrera. I'm a clinical endocrinologist and a diabetes researcher with over 20 years of experience in the field. I also run a large advanced diabetes practice in San Antonio, Texas, which is a state with one of the largest rates of diabetes in the United States. Lexicon paid for my travel, and I'm not receiving any honoraria or being compensated for my time, and I'm here to represent myself and thousands of patients with type 1 diabetes that we have in Texas.

Today, 42 million adults in the United States live with diabetes, and this global pandemic continues to grow at an alarming pace. It is a leading cause of blindness, amputations, and end-kidney disease in the world; however, cardiovascular disease, heart failure, heart attacks, and strokes, we continue to forget remains the leading cause of death among patients with diabetes.

In the past few years, we have discovered

new classes of diabetes medications that not only improve glycemic control, but also provide cardiovascular protection, reduction in heart failure, hospitalizations, decrease the progression of kidney disease, dialysis, and death. However, these therapies are only FDA approved for patients with type 2 diabetes, leaving those with type 1 diabetes vulnerable to increase risk of cardiovascular events, severe complications, and death.

It has been over 100 years since the discovery of insulin, and as of today, it continues to be the only effective medication approved for type 1 diabetes management. Insulin unfortunately does not protect against cardiovascular events, and this lack of additional pharmacological and cardioprotective options leaves a critical gap in care for patients with type 1 diabetes. Sodium glucose transporter inhibitors have emerged as a promising class of drugs, showing not only benefits in glycemic control, blood pressure, weight loss, but most importantly provide cardiovascular

protection, including reduced risk in heart attacks, strokes, heart failure, and death.

My research in the last 10 years has focused in understanding the mechanisms behind the cardioprotective effects of SGLT2 inhibitors, and we have shown that these medications are effective in patients with type 2 diabetes and that the cardioprotective and renal effects are independent of glycemic control. As we heard, patients with type 1 diabetes without proper management can develop, or may develop, diabetic ketoacidosis. SGLT2 inhibitors have shown to mildly increase these risks; however, the absolute numbers are low in clinical trials, and these risks can be mitigated with proper medical management and education.

In summary, there's a large unmet need for medications that promote not only effective glycemic control, but also, and most importantly, decreased cardiovascular risk in patients with type 1 diabetes. This is a frail and high-risk population that has been forgotten for many years,

and it has come to a moment, with the latest classes of drugs like SGLT inhibitors, we'll be able to decrease complications, cardiovascular events, medical costs, and death in our patients.

DR. LOW WANG: I'm sorry. We're over time.

DR. HERRERA: Thank you very much for your time and attention.

DR. LOW WANG: Thank you.

Speaker number 21, please state your name and any organization you are here to represent for the record. You have 3 minutes.

MS. HOHMANN: Good afternoon. My name is Kristen Hohmann. I'm a member of a patient advisory board for another pharma company in a different therapeutic area. I have no other interests or conflicts, and I'm here representing myself. I very much wanted to attend in person, but I'm only 11 weeks post a simultaneous kidney and pancreas transplant, and was advised against traveling at this time.

I was diagnosed with type 1 diabetes at the age of 9. Next week, I will have lived with this

demanding 24-7 disease that has dictated my entire life and its complications for 35 years. Because of my diabetes, I have experienced neuropathy; proliferative retinopathy; macular edema; hypertension resulting in cardiovascular damage; and most significantly, chronic kidney disease, which recently led to the need for a kidney transplant at 43 years old.

When I learned about the severity of my CKD last year, I began researching, and discovered the number of medications that exist to treat and prevent CKD and CVD and the wealth of clinical evidence supporting their benefits. I also learned none were approved for those with T1D, only T2. I saw several providers until I found one willing to prescribe an SGLT2 inhibitor off label.

I was made aware of the risks and side effects, and educated about necessary precautions by my provider, and never experienced any issues or complications. In fact, I credit the medication with lowering my A1C, regulating many of my labs, and slightly improving and keeping my kidney

function stable so that I was able to avoid having to go on dialysis before transplant.

My transplant journey has not been an easy one. I received both organs in my first surgery, followed by a hypertensive crisis and pancreas failure the next day. My new pancreas had to be removed, and the day after, I was offered a second pancreas and underwent my third 7-hour surgery within 3 days. Two weeks later, I had a rejection where, thankfully, my second pancreas was able to be treated and saved.

I'm beyond grateful to my team and donors for this gift of life but sometimes find myself wondering, if this sort of medication had been available to me at an earlier stage in my CKD, maybe I would have not had to go through this excruciating experience that has left me on an intensive medication regimen and immunocompromised for the rest of my life.

For me, it's too late, but for the many people living with type 1 and CKD, it isn't. People with T1D should have the option to weigh the

potential benefits and risks of this class of drugs and engage in shared decision making with their provider. For me, it was worth it, and others should have that same opportunity earlier in their disease, where it can make a real difference and even change the course of their entire life. The possible risks are the same type of risks a type 1 is perfectly capable of and already managing on a daily basis. Thank you very much for your time and consideration.

DR. LOW WANG: Thank you.

Speaker number 22, please state your name and any organization you are here to represent for the record. You have 3 minutes.

DR. FLEMING: I'm Alexander Fleming, an endocrinologist and member of Conexa, a firm that supports the development of regulated products, especially for diabetes. I have no conflicts of interest, nor have I been compensated for appearing today. I once advised the sponsor prior to the original NDA submission, but I have not since been involved or in contact with the sponsor.

I start by affirming both FDA and the sponsor for expertly doing their respective jobs with professionalism. It was a close call on the original NDA submission, but it proved to be the right decision to withhold the general type 1 diabetes indication. With the benefit of time, we now have a solid basis for a product label with the proposed indication for the smaller, well-defined population.

To be sure, a positive benefit-to-risk decision does have to stand on the evidence, both available and what is not available. I would only point out secondary considerations that favor a positive judgment. First, the adversities of primary relevance, DKA and severe hypoglycemia are well defined, identifiable, and manageable for purposes of safety surveillance of real-world use.

In general, people with type 1 diabetes have the full attention of their disease and are highly motivated to be informed and to take care. People with type 1 diabetes are helped by a team of specialists who themselves are highly informed and

motivated to take care. As you have just heard, people with type 1 diabetes do want options to minimize risk of complications and death, and in using them, they will take care.

Three appropriate questions and concerns persist about the benefits and risks of Zynquista for the proposed indication, but I'm confident that appropriate labeling and risk management can be devised by the company and FDA to provide access to the indicated population. We can expect that in the clinical use and oversight of this drug, all stakeholders involved, and especially people with type 1 diabetes, will take care. Thank you for your service.

DR. LOW WANG: Thank you.

Speaker number 23, please state your name and any organization you are here to represent for the record. You have 3 minutes.

MR. SJOLUND: Hi. Good afternoon. My name is John Sjolund, and I'm in San Diego, California. I am the CEO of Luna Diabetes; however, I'm here in a personal capacity to advocate on behalf of all of

those of us living with type 1 diabetes, and I have not received any compensation of any sort to be here today.

I have lived with type 1 diabetes for 38 years now. I'm one of the lucky ones that is able to meet A1C goals, but it is a grind for me. Diabetes for me, and all these people living with it, is a struggle. I deal with high and low glucose multiple times per day. When I see a plate of food or a snack, I see a math equation ahead of me, not just a delicious meal. I get a new glucose reading 288 times per day, and I spend at least one hour each and every day dealing with my diabetes, and thinking about it, and thinking how I can do the best that I can. People commonly say that people living with diabetes think about it 4 to 500 times per day. Diabetes is a grind, and it requires constant vigilance.

Insulin, while life-saving, is currently the only FDA-approved option for those of us with type 1 diabetes, and it is falling short of fully managing the disease for most people.

Sotagliflozin provides desperately needed help to those of us living with type 1 diabetes. I know nearly a dozen people with type 1, if we had been lucky enough to access these medications off label, and they describe it as life-changing, less insulin, less fewer glucose excursions, much less time spent managing their diabetes and worrying about the results. Most of them are calling it a miracle medication for their day-to-day glucose management. You would think that would be enough, but then we're also seeing and we have heard today about the kidney protection, the reduced risk of cardiovascular disease; it's pretty incredible.

Now, I and everyone in this room is well aware of the concern about euglycemic DKA and the risk that it entails; however, I can share that I would do almost anything to spend less time per day managing my disease. Since the early use of SGLT2s in diabetes, there's been a lot of work done, including the STICH and STOP protocols, to educate those of us with the disease on how to manage that risk, and we've heard today, everyone who's living

with diabetes has thought that it's, by far, an acceptable risk. It's a small price to pay to monitor for symptoms of DKA and to be prepared for ketone tests for the incredible benefits, not to mention that continuous ketone monitoring seems to be coming in our very near future.

I believe with proper education and labeling, it is very manageable. So in closing, I'm here today advocating for those of us living and struggling with type 1 diabetes to have access to better treatment options. I'm advocating the FDA to approve sotagliflozin for type 1 diabetes. Thank you.

Clarifying Questions (continued)

DR. LOW WANG: Thank you.

I'd like to thank each and every speaker for our open public hearing. The open public hearing portion of this meeting has now concluded. We will no longer take comments from the audience.

So we actually have the slide available from the applicant that was asked for by Dr. Everett, so if you could please show that.

DR. VADUGANATHAN: Muthia Vaduganathan, Brigham and & Women's Hospital. For orientation, these are the baseline characteristics of the SCORED long-term outcomes trial in type 2 diabetes and chronic kidney disease juxtaposed against the inTandem trial population baseline characteristics. By design, patients in SCORED had reduced GFR below 60 compared with the T1D-CKD subgroup of the inTandem population.

We already discussed that there was about a two-decade difference in these two populations. Beyond that, there are several comparable characteristics. Gender was balanced across all three of these trial populations; furthermore, the majority of patients were overweight or obese. Patients with type 1 diabetes had much longer disease duration, and in keeping with that, their overall cardiorenal markers were also similarly elevated.

For instance, their hemoglobin A1C -- if you compare that in the SCORED trial compared with Study 312, which lacked the prior insulin

optimization -- is highly comparable. Furthermore, the median UACR, the key marker of cardiorenal risk, is in the same range of 50 to 80. Many patients in both trials were treated with renin angiotensin system inhibitors in the background.

DR. LOW WANG: Great. Thank you.

Dr. Everett, do you have any questions about that?

DR. EVERETT: No, that's great. Thank you for providing those data.

Questions to the Committee and Discussion

DR. LOW WANG: Great.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and the 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. After I read each

question, we will pause for any questions or comments concerning its wording.

The first question is a discussion question. Discuss the evidence and uncertainties based on the existing clinical trial data as to whether sotagliflozin improves A1C across a range of estimated glomerular filtration rates, or eGFRs, including the following categories: 45 to less than 60; 60 to less than 90; and 90 or above. Consider the durability of the treatment effect demonstrated.

Are there any questions or comments about the wording of the discussion question?

(No response.)

DR. LOW WANG: Okay. So if there aren't any, we'll go ahead and open this question to discussion.

Go ahead, Dr. Newman.

DR. NEWMAN: Thank you. From looking at the data --

DR. LOW WANG: Can you go ahead and state your name?

DR. NEWMAN: Oh, sorry. Dr. Connie Newman. I think that what we saw when we looked at the data, at least what I got out of it, was that there is an improvement, or was an improvement, in hemoglobin A1C of about maybe 0.3 to 0.4 percent, on average, in the categories of 60 to below 90 and above 90 for estimated GFR, but there was some uncertainty about whether the reduction in hemoglobin A1C in patients with GFR of 45 to 60, whether that was significant, and I think that was due to the low patient numbers.

In terms of the durability of the treatment effect, the available data questioned that, but I don't think that has been adequately evaluated. Thank you.

DR. LOW WANG: Thank you.

Mr. Tibbits?

MR. TIBBITS: Mr. Tibbits. I think I'm in alignment with Dr. Newman. I certainly feel the same way about the two higher eGFR groups. The lower group, with the numbers that we're looking at, I used to be involved in chronic disease

trials, and that sort of looks like a chronic disease trial -- I mean, sorry, a rare disease trial. So it's really hard to tell what that impact is. I think, later, I would urge Lexicon to pay specific attention to that group and do additional studies/trials with that group because, certainly, there is great unmet need with that group, but I don't think we have enough data to know what the impact is.

In terms of durability, I would say, do we know? Not necessarily, but I would say 52 weeks of having a lower A1C is better than zero weeks of having a lower A1C. So I think, for me, durability of one year is better than having a higher A1C for that one year. Thank you.

DR. LOW WANG: Dr. Everett?

DR. EVERETT: Thanks. Brendan Everett. I'll focus my comments on the 24-week study data because it seems to me that that's when the end of the blinded treatment period happened for 309 and 310, and also 312; and after that point, at least -- and if I'm wrong, I'm happy to be

corrected. But just from the FDA's presentation, it seemed like after that point, physicians and patients were unblinded both to what their A1C levels were and whether or not they could then have adjunctive therapy continued. So the insulin therapy intensified, for example, to improve their control.

So I think it's appropriate to focus, in terms of the change in A1C, on the primary outcome in the labeling indication on the 24-week outcomes. And I agree with what Dr. Newman said, that there seems to be about a .03-.04 percent reduction in hemoglobin A1C. I think as a clinical trialist, you're generally taught to take the point estimate that's true across the entire trial, and the times -- in fact, this was Dr. Califf who taught me this; that if there are exceptions to that, it's pretty unusual that the point estimate varies in a significant way within individual treatment groups.

Now, we have a pathophysiologic reason why there might be less hemoglobin A1C reduction in those with less renal function given the mechanism

of action of sotagliflozin, but nonetheless, I think if you you look at the data at 24 weeks from 309 and 310, in a small number of patients, the point estimate for the reduction in hemoglobin A1C in the less than 60 group was minus 0.27 and minus 0.21 for the two different sotagliflozin doses, and those compare and seem awfully similar, to me, to the eGFR of greater than equal to 90 where the estimates are 0.28 and 0.28. So if you take the overall principle that you really have to demonstrate profound differences to intuit that they're there, that looks similar.

Now, 312 is not quite as in line, the differences maybe are somewhat larger, but I share the concern and the rationale that the FDA has, and perhaps the sponsor as well, that when the eGFR drops less than 60, the efficacy with respect to that particular outcome, hemoglobin A1C reduction, may be somewhat diminished. I'm actually not sure that the data that we've been presented conclusively demonstrate that they are, so it seems to me that, on balance, you take the net overall

treatment effect in the entire randomized trial as the default when that's the case.

DR. LOW WANG: Thank you.

Dr. Konstam?

DR. KONSTAM: Yes, I totally agree with Brendan. Just to follow up on it, we usually look at subgroups for consistency, or lack thereof as he suggested. Looking at these data, one point to be made is we have not proven that the low eGFR group is different than the other two groups; however, the trend is concerning, or perhaps it is. So that's the way I would say it, and I think we can't say much more than that.

DR. LOW WANG: Thanks.

Dr. Wang?

DR. WANG: Yes. Thomas Wang. I have very similar impressions regarding the data. My general gestalt is probably the hemoglobin A1C is similar across the different eGFR groups; certainly, no evidence that it's better in the lower eGFR group. And, obviously, because of the conference intervals there, there is significantly less precision in the

lowest eGFR group.

The only other comment I would make, and it's really more of a question, and I don't know if it's answerable, is given that the original TANDEM studies were done seven years ago now, when I assume the penetration of CGM, and the closed-loop systems, and all the devices that we have today was less, I do wonder whether these point estimates from 2017 even still apply today; and if they don't, in which way they would go. I would assume that the advent of new devices has improved for baseline glucose control such that the window for improvement might even be slightly narrower.

DR. LOW WANG: Dr. Newman?

DR. NEWMAN: Connie Newman. Thank you. I just want to clarify what was said about the low eGFR group below 60. Because the numbers were small, I believe the confidence interval is very wide, and you can't exclude a very small increase in hemoglobin A1C. But I do think that if there were more patients, that would not be the case; that there would be a benefit in terms of

hemoglobin A1C reduction in that group.

DR. LOW WANG: Cecilia Low Wang. I felt like, as was mentioned, the sample sizes were extremely small, and there were lots of differences between the combined pooled 309-310 trials and 312. I think that made it extremely difficult to draw conclusions.

It did look like sotagliflozin lowers A1C in patients with GFR greater than 60, but the effect seems to be attenuated when the GFR is less than 60. It doesn't seem like the 400-milligram dose has a greater effect. And then in the 310 trial, I thought that was pretty problematic because there wasn't really significant A1C lowering in that kind of GFR subgroup; and I agree with Dr. Everett that I think it's hard to make conclusions with the 52-week data because those were unblinded, and that was beyond the the primary endpoint.

So overall, I think there may be a difference in A1C lowering at that GFR threshold of 60 with less lowering below 60, and there's not strong evidence of durability at 52 weeks, is the

bottom line, is what I see.

Are there any other comments from the panel?

Go ahead, Dr. Nason.

DR. NASON: Thanks. Martha Nason. I just wanted to explicitly say one thing that a lot of people have sort of inferred but nobody's said outright, which is that this is an ad hoc subgroup, as far as I know anyway, and it was not predefined. So it makes you wonder -- and I don't have an answer to this; I'm not sure anyone does -- what other subgroups might have been considered instead and how to adjust for that mentally as far as the ability to pick out subgroups where things seem different.

I'm sure everyone around this table knows the concerns with multiple comparisons and the ability to find that something works better in Virgos than Libras who are left-handed if you look hard enough. And I'm not saying that's what's happening here, but it's certainly something that any ad hoc subgroup raises, a specter that it raises, and that it needs to be, I would say, a

pretty strong and biological effect to split it rather than lump it, to agree with my colleagues to my left.i

DR. LOW WANG: Alright. Thank you.

If there are no other comments -- oh, is there another person with a comment?

(No response.)

DR. LOW WANG: Okay. If there are no other comments on this discussion question, I'm going to go ahead and summarize before we move on to discussion question number 2.

I think that, in general, the panel discussed the fact that the data presented were not conclusive but the trend was concerning. As was mentioned by Dr. Nason, this is not a predefined subgroup. It was ad hoc. The sample sizes were small. There was no accounting for multiple comparisons. There does appear to be A1C lowering across the eGFR categories, especially with the 60 to less than 90 group. There's more uncertainty in the A1C lowering for the GFR less than 60 group, but that sample size was extremely small. It's

about a tenth of the size of the rest of the group. In the durability, we really can't comment on that very well. It's unclear. The data beyond 24 weeks was unblinded, so difficult to draw conclusions.

Let's move on to discussion question number 2. This is also a discussion question. First, I'll read the question, and then see if there are any issues with the wording of the question.

Question number 2, discuss the evidence and uncertainties as to whether patients with type 1 diabetes and chronic kidney disease accrue a greater benefit with respect to microvascular disease than patients with T1D without CKD for any given reduction in the A1C.

In your discussion, consider different KDIGO categories of CKD, classified by both GFR -- so the categories are 45 to less than 60, 60 to less than 90, and then 90 or above -- as well as the UACR, less than 30, 30 to less than 300, and 300 or higher. Discuss the magnitude of clinical benefit conferred by the A1C reductions expected with the

use of sotagliflozin across the range of CKD severity, considering both eGFR and UACR.

So are there any questions about the wording of this discussion question?

Go ahead, Dr. Everett.

DR. EVERETT: So this is specific to the eGFR reduction that we're seeing with sotagliflozin and its beneficial effects on --

DR. LOW WANG: Go ahead, Dr. Archdeacon.

DR. ARCHDEACON: So you're saying what clinical benefits are we talking about?

DR. EVERETT: This question seems narrowly constructed to really be talking about whatever reduction in hemoglobin A1C we see with sotagliflozin, which we just finished talking about, and what are the benefits on kidney function --

DR. ARCHDEACON: We've broadened it to microvascular, so if you want to speculate on retinopathy --

DR. EVERETT: Okay. Fine.

DR. ARCHDEACON: -- but we're not talking

about non-A1C mechanistic issues.

DR. EVERETT: Just [indiscernible 6:44:26].

DR. ARCHDEACON: Right.

DR. EVERETT: Okay. Thank you.

DR. LOW WANG: And just one more clarification on this discussion question. When you talk about discussing the evidence and uncertainties, you're talking about even outside the trials that were presented.

DR. ARCHDEACON: We'll certainly accept your expertise if you have something to base this on. We were able to present some data from PERL, and the Joslin Proteinuria Cohort, and DCCT, but if you have other expertise, including your clinical acumen, that's reasonable for you to draw on.

DR. LOW WANG: Okay. Terrific. Great.

Any other questions or issues with the wording?

(No response.)

DR. LOW WANG: Okay. If not, then I'll go ahead and open this discussion question for comment.

Dr. Konstam?

DR. KONSTAM: Yes. I think the answer is we don't know. We don't have any evidence for it. I think the group was chosen on the grounds that they have higher rates of microvascular and other complications, therefore stand more to benefit. Point of fact, if you have a greater risk of those events, then the absolute improvement would be better for any hazard reduction; however, in fact, we cannot go from the fact that this is a group that has greater risk to saying, ok, if we improve glycemic control, that risk will go down. So I just don't think that we have any evidence one way or another on that subject.

DR. LOW WANG: Thanks.

Dr. Onumah?

DR. ONUMAH: I have to agree with the doctor who just spoke because even when we --

DR. LOW WANG: If you could please just state your name.

DR. ONUMAH: Oh, sorry. Barbara Onumah. I agree with the statement that was just made because

when we look at the data that we have, even from the PERL study, which has some objective numbers, it says that the reduction of A1C that we see in the TANDEM trials of 0.3 to 0.4 percent, you'd have to have a sustained 10-year reduction in A1C of 0.3 to get an improvement in eGFR of 1.6 to 2.4.

Now, that's important, but that does not translate into a significant improvement in renal function. So I think we don't have enough information to have a conclusion on this discussion point for that question.

DR. LOW WANG: Thank you.

Dr. Newman?

DR. NEWMAN: Connie Newman. I just wanted to say that I agree with what has already been said. We don't have enough data, and I don't think there's enough data in the literature either to say there were other clinical benefits.

DR. LOW WANG: I would say that we have strong evidence of benefit for reduction in microvascular disease risk in terms of eGFR decline; development of albuminuria when we have

good glycemic control, especially in patients with microalbuminuria, higher A1C, or in macroalbuminuria, and that's what the DCCT showed us. It looks like there's a potential greater benefit for microvascular disease reduction, but I don't know if it's for any given reduction in A1C. I just don't feel like the data demonstrate that in patients with T1D and CKD compared to those without CKD.

I think SCORED showed us that there's greater absolute risk reduction for the composite kidney endpoint with a GFR of greater than 45 or with microalbuminuria, which is in contrast to the CKD population in this proposed indication, but this magnitude of benefit seems to be pretty small across the range of the eGFR categories in terms of the renal endpoint. Number of events was incredibly small, so I feel like it's really impossible to draw conclusions about this.

Dr. Yanoff?

DR. YANOFF: Thank you. I wanted to clarify, the any given reduction A1C was thinking

of previous version slashed, but I want to emphasize that's not really the point of the question. We're not asking you to consider ranges of 0.1, all the way to what was seen in DCCT as 2 percent. We're just really talking about the range that you'd expect with sotagliflozin, so about about 0.2 to 0.3 percent, and if you believe that that much difference in A1C that would be expected to be conferred by sotagliflozin would make a difference in these different populations. So it's not as broad as do we know everything about every given A1C. I don't know if it helps.

DR. LOW WANG: I think what you're maybe saying is the 0.3 or 0.4 percent reduction in A1C more beneficial in patients with T1D and CKD compared to people without CKD?

DR. YANOFF: Correct.

DR. ARCHDEACON: I think I drafted the question or participated. What I had in mind was imagine, for instance, three different patients. There's somebody who has an eGFR of 100 and no evidence of proteinuria, somebody who has an eGFR

of 90 and a microalbuminuria of 40, and then somebody who has an eGFR of 85 and macroalbuminuria. Each one of them has a reduction of 0.3. Is there any evidence to say that that 0.3 helped any of those three people more than any of the others?

DR. KONSTAM: Can I respond?

DR. LOW WANG: Dr. Konstam?

DR. KONSTAM: Again, my answer would be that you have to separate potential hazard reduction from potential absolute risk reduction. I think the fact that the patients with the lower eGFR I think have greater risk for microvascular disease, that would translate into any given hazard reduction that you would get to a greater absolute benefit, is really the reality of it. But you have on top of that that there's a trend toward reduced glycemic control in the lower eGFR group. I think a group that has a higher risk has a greater likelihood of benefiting from an absolute improvement basis.

DR. LOW WANG: Dr. Wang?

DR. WANG: Thomas Wang, just stating my thoughts for the record. I agree with all the prior comments. I find, as Dr. Konstam articulated, that this question is important but difficult to really achieve a conclusion on the basis of the data that currently exists.

If you take one approach, which is the one he articulated, which is to say, well, let's say that the relative risk reduction was similar in people with and without CKD, then on the basis of that, because we assume that people with CKD have a higher absolute risk than by inference, the patients with CKD will experience a greater absolute risk reduction.

I think that on the face of it seems plausible. That being said, in answering question 1, many of us weren't sure that the initial reduction was exactly the same across all these groups, so that introduces uncertainty into that.

I guess the other way to approach it, which I think the FDA nicely laid out using the study

that has been cited multiple times, the PERL study, is to try to extrapolate from observational data with all of the pitfalls of that. And I have to say I was somewhat surprised at the relative modesty of benefit if you use that approach, that you drive something like a 1 and a half to 2 and a half unit change over 10 years in eGFR.

So again, I don't find, when I think about the different ways of approaching this, an answer that gives me a high degree of confidence that we have enough data to move forward.

DR. LOW WANG: Cecilia Low Wang. I just want to mention that in terms of trying to use the PERL study or the PERL data to draw conclusions, the PERL study did not show any significant improvements in A1C. A1C was the same at baseline as it was at the end of the trial. So the way we're using it is actually cross-sectional; it wasn't a treatment trial for A1C.

So I don't think that we can draw conclusions from the PERL trial for that. We can see that there's worse kidney outcomes in patients

with higher A1C and with stage 2 and stage 3 CKD, but other than that, I don't know that we can say that decreasing the A1C by 0.3 percent is going to give you more benefit in someone with CKD rather than someone without.

We have more comments.

Dr. Everett?

DR. EVERETT: Brendan Everett. I just want to echo what Dr. Wang and Dr. Low Wang just said. I actually don't find the PERL data to be helpful at all because I think it's an observational analysis, and there's no surprise that people who have slightly worse A1C control at baseline have a progression in their kidney function at a more rapid rate than those who don't. It's not an interventional trial where we can really conclude anything. I think just a remarkable paucity of data here to have any confidence.

I guess my gestalt, and you can take this for what it is, which is a cardiologist's opinion, is that an A1C reduction of 0.3 percent seems pretty modest and unlikely to have, at least to me,

a substantial direct benefit on something like eGFR. I could be wrong. I don't think there's a huge amount of data. I think there are other potential benefits that are not specific to this question that I'm sure we'll discuss in a moment.

DR. LOW WANG: Dr. Seliger?

DR. SELIGER: Thanks. Steve Seliger. Yes. I think a lot of this goes back again to the specific subgroup that the sponsor is requesting consideration for, and maybe back to some of our comments from the morning. The group of individuals with type 1 diabetes and an eGFR of 60 to 89, let's say who don't have at least A2 albuminuria, that is actually not a group that is associated with an increased risk of end-stage kidney disease, generally, and it's also not a group that has been studied even in other situations, type 2 diabetes or non-diabetics, for the effects of SGLT2 inhibitors on end-stage kidney disease progression at all.

So I find that the evidence base for that, just generally, for this intervention, or even for

any specific intervention, to slow progression, the data would be extremely uncertain. Perhaps the argument is most compelling for those with higher levels of albuminuria, but those are the kinds of patients for whom there were very few in the TANDEM database. There's really the crux of it all.

DR. LOW WANG: Thank you.

Dr. Parsa? Oh, sorry -- Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: I put my card down because other people already brought up my point.

DR. PARSA: I was just going to second exactly what you said. Again, from a nephrologist standpoint --

DR. LOW WANG: Yes. Sorry about that.

DR. PARSA: -- one, I don't think we can read too much into the PERL study, and we haven't really looked at a population of patients in all of our discussions that could potentially have that big benefit with even a smaller hemoglobin A1C reduction.

DR. LOW WANG: Thank you.

Dr. Irony?

DR. IRONY: Thank you. Ilan Irony. I think I agree with all the comments here about uncertainties, and there are plenty, of how to infer from the observational part of the PERL study into what we try to conclude here for sotagliflozin. But in response to the magnitude of the A1C reduction that Dr. Everett mentioned, that this is relatively small, I agree, 0.3, 0.2 is relatively small. But we have to remember that this is coming from a baseline of people that are relatively well controlled compared to the general type 1 diabetic population. Even though the entry criteria was up to hemoglobin A1C of 11, the average was 7.7 or so at baseline, so you don't expect much of that.

But my question here is -- and I know the FDA's consideration in the briefing book is that the time in range is not something that is an endpoint being considered because hemoglobin A1C and capturing inaccurate terms in a study, the degree of hypoglycemia is sufficient to cover the concept of time in range. But from what we hear

from the patients in the open public hearing and so forth, what kind of consideration FDA would say is an additional benefit of having peace of mind in terms of glycemic control, based on time in range compared to what's captured only in hemoglobin A1C?

DR. YANOFF: FDA is always open to any data that supports a clinical benefit of drug, how a patient feels, functions, or survives. So how a patient feels with better time in range, if there was a way to quantify that, then FDA has always been open to that.

DR. ARCHDEACON: I think we've signaled in our recent guidance, for instance, that even though A1C is often the basis of a regulatory action, if time in range data is rigorously collected and it aligns with what the A1C data shows, we would also include that in a label. I think for purpose of this discussion, I do think we have pretty rigorous hypoglycemia data and pretty rigorous A1C data, so the time in range seems somewhat duplicative, but if you have found it to be helpful beyond what -- you're certainly encouraged to consider

that.

DR. IRONY: No. I acknowledge here the data on time in range because the number of people on CGMs was a small fraction and the data are sparse. But I think it's something that we hear from experience of off-label use outside the trial, that time in range, in general, leads to more peace of mind in terms of fluctuation.

DR. YANOFF: As an industry rep, I really appreciate your comment, and I encourage you to ask industry to develop a tool that will be able to assess how a patient feels with improved time in range, and FDA would be happy to consider that.

DR. LOW WANG: Thank you.

Any other comments from the panel on this discussion question?

(No response.)

DR. LOW WANG: Okay. I'll go ahead and try to summarize our discussion, and definitely, if I've missed anything, please add to it. I think what was said was that there's a distinction between relative and absolute risk reduction. So

in terms of what are we talking about here, we think that a higher risk population does have a greater potential for benefit, but you're unable to extrapolate any conclusions about whether or not there is truly greater benefit with a certain level of A1C reduction from the data that we have.

So there are potential other benefits, but those aren't quantified. So overall, it's really difficult to conclude from the available data, and we don't have the evidence, there's a lot of uncertainty, and the magnitude of benefit from this small improvement of A1C is expected to be small. We just don't have enough.

Any other additions to that summary?

(No response.)

DR. LOW WANG: Okay. Let's move on to discussion question 3. I'll read the question and see if there are any issues. Discuss whether the magnitude of the DKA risk in patients with T1D and CKD using sotagliflozin has been sufficiently characterized. Discuss the evidence and uncertainties regarding DKA risk for patients with

T1D and GFRs in the following ranges: 45 to less than 60, 60 to less than 90, and 90 or greater.

Any questions about the question?

Go ahead, Dr. Roy-Chaudhury.

DR. ROY-CHAUDHURY: Prabir Roy-Chaudhury. I'm not sure whether this is the exact place but, to me, the most important thing that isn't here is the risk of DKA in a 17 year old on sotagliflozin and the risk in somebody who is in a totally different state; in other words, somebody who's really compliant versus somebody who's not. Definitely in the discussion, I want to raise that, but I'm not sure whether that should be the question as well.

DR. ARCHDEACON: If you'd like FDA to comment, I guess I will. The way that I look at it is the applicant has come up with a labeling strategy, so the labeling strategy is suggesting that they will identify patients who have CKD, and on that basis give them the drug. If they were proposing a different strategy that was based on age, we probably would have phrased the question

differently.

Now, it may be that you're willing to assume that providers, in addition to following the labeling, they'll be informed by what they know about in general patients, and perhaps even what they know about that individual patient. I think some of the speakers have talked about how they know a lot about their individual patients that they're working with. Obviously, you can consider that as well, but the reason we framed the question as we did is because this appears to be the labeling strategy which anyone would follow.

DR. LOW WANG: Any other questions about the wording?

(No response.)

DR. LOW WANG: Alright. So then, I'll open this discussion question to panel comments.

Dr. Konstam?

DR. KONSTAM: Well, I think a couple of things. I would say one is that, looking at the data, it does appear that there's a trend toward less DKA in the eGFR group between 60 and 90, so

there's a trend. The confidence intervals overlap, and I'm sure there's no treatment by subgroup interaction that's significant in there, but it's trending in that direction.

The other thing I would say, though, in general, I'm struck still with the Sentinel data. Obviously, that was not a controlled trial. You have nothing to compare it to as you do with treatment versus placebo; however, looking at the absolute numbers, those absolute numbers are higher than in the treatment group and these data in the trials, and that concerns me. It shows what I guess I would suspect anyway, that the rate of DKA is going to be higher in the real world than it was in those trials. So I continue to be uncertain about, really, what the level of DKA risk is.

DR. LOW WANG: Thank you.

Dr. Chrischilles?

DR. CHRISCHILLES: Just responding to that, I actually --

DR. LOW WANG: Sorry. Could you state your name, please?

DR. CHRISCHILLES: Betsy Chrischilles. Actually responding directly to that, I don't read the Sentinel data quite the same way just because I think the average follow-up time is just about 3 months in the Sentinel data, and we're looking at rates per hundred person-years. So I think if we actually look at the number of cases --

DR. KONSTAM: I thought the Sentinel data that we looked at was rate, 100 patient-years. There's a graph in your briefing document.

DR. LOW WANG: Could the FDA go ahead and show that slide?

DR. CHRISCHILLES: Oh, ok.

DR. CHANG: Po-Yin Chang, Division of Epidemiology. I think that's correct. In Sentinel, the follow-up of the insulin use in Sentinel is about 0.3 years, but overall, we censor patients for a year only. So we follow them, and if they have a DKA event, we censor and if they don't have DKA event, and then follow up, and up to one year we stop the follow-up.

I would like to point out some perspective

that clinical trials are very well-controlled studies, so they have all the measurements in place to reduce the risk of potential hypoglycemia and DKA, for example. But in clinical practice, I'm not sure people who have contributed to the claims data have this same approach to reduce DKA or hypoglycemia. So I'm cautious to compare trial results to the clinical real-world data results.

DR. CHRISCHILLES: But just to finish, if I were to do that, I would take those rates per hundred person-years of around 9 and divide it by 4 to get to a 3-month rate, just if I were going to do it back of the napkin. I know we can't compare, but I wouldn't say we could conclude that it's high.

DR. LOW WANG: And go ahead and state your name before you comment.

DR. KONSTAM: Marv Konstam. I'm just looking at the FDA briefing document, figure 6, that shows the DKA cases per hundred person. The Y-axis is DKA cases per hundred patient-years, so somehow, they are adjusting it to be comparable, is

my reading.

DR. LOW WANG: Go ahead.

DR. PENZENSTADLER: Hi. This is Justin Penzenstadler. Can we go to slide 118? I think I can present that for the panel. That's slide 118 in the FDA deck.

Dr. Konstam, is this the data you were referring to? Thank you.

(No audible response.)

DR. LOW WANG: I think it's the Sentinel data for DKA incidence across GFR categories.

DR. PENZENSTADLER: Yes. Can we go to FDA slide number 58, please?

DR. WANG: If you back up even to slide 53, I think Dr. Konstam's point, which I share, is that those rates are much higher than the rates in the trial, which is the source of his concern.

DR. KONSTAM: Mark Konstam. There are clearly limitations in the type of analysis you can do because it's observational, not a controlled trial. But I was just looking at the absolute rates in the active treatment group in the trials

compared to the rates in Sentinel, and they appear that the Sentinel rates look the higher to me.

DR. LOW WANG: Absolutely.

Alright. Dr. Newman?

DR. NEWMAN: Thank you. Connie Newman. I just wanted to go back to the question and say that I think there is a seriously increased risk of DKA in this patient population, and we can't forget that. Whether it's been properly characterized in the different eGFR groups is still uncertain. I think if we had more data, we would know whether there's any difference, like more DKA in patients with lower GFR, but I don't think we see that in the data available. I just want to remind everyone that DKA is life-threatening and is an extremely serious adverse event.

DR. LOW WANG: Dr. Parsa?

DR. PARSA: Afshin Parsa. I'll keep it short, but to say that I also agree with the points that have been made and why I had my question earlier in terms of the absolute risk of DKA not being clear to me. And part of it is, yes, the

Sentinel data is not perfect, but it's hard to ignore, and the data from the clinical trial, both in terms of numbers and the selection of population, pretty much make it very challenging.

I've been struggling for days trying to figure out what the risk of DKA really is, and one was the severity question, and one the actual rate, what would be expected in the real world. And I still don't have an answer, which makes this hard because at the end of the day it's a risk-benefit ratio, so I find it insufficient.

And similarly across the GFR ranges, at least based on the data from here, I think go back to what was mentioned before, breaking down into different subgroups and the confidence intervals get wider, and it becomes a little bit unclear. And the claims data, now there is a bit more of a difference there but, again, that's a different population.

DR. LOW WANG: I would say that I think the DKA risk with sotagliflozin in patients with type 1 diabetes and CKD is insufficiently characterized

across the categories, but the available data really suggest that CKD may be associated with an increased risk for DKA per the Sentinel data, as well as the FinnDiane data. It's possible that the T1D exchange doesn't show that, but it looks like maybe a different population. It's also difficult to know how the DKA episodes were ascertained, so there could be a lot of missing data there.

But I think we have also comments from Dr. Wang.

DR. WANG: Yes. Thomas Wang. Again, just stating for the record that as the prior panelists have noted, clearly there's increased risk of DKA associated with the medication; no one disputes that. Across the GFR categories, I do think it's a little bit unclear, but there does seem to be the possibility, purely based on a higher potential baseline risk of DKA in those with a low eGFR, that there might be a higher absolute risk of DKA with this drug in that group that interestingly, to me, parallels the argument of potential greater benefit in the same group, and is also similar in that the

magnitude of increased benefit or increased risk, to me, are similarly uncertain. So both sides of the equation, at least in my reading of it, there's substantial uncertainty.

DR. LOW WANG: Thank you.

Dr. Everett?

DR. EVERETT: Thank you. Brendan Everett. I think there's a considerable uncertainty as to what exactly the magnitude of DKA risk is in patients with type 1 diabetes and CKD. I think we all agree it's higher. I think there is insufficient evidence, in part, because when you do a trial in a development program with an outcome like hemoglobin A1C, and you stop a trial after 24 weeks, you don't have sufficient time and exposure to the drug to actually collect adverse outcomes that happened at a lower frequency.

I was interested to see what the event rates were in the trial. We have estimates of 3 to 6 events per hundred patient-years, approximately, an observation, and as a cardiovascular clinical trialist who tries to

design trials to collect patients who are at high enough risk to have cardiovascular events during the course of follow-up, 3 to 6 events per hundred patient-years is a great target in terms of collecting a group of patients who are sick and are likely to suffer a potentially fatal event.

So I think that rate of DKA gives you some sense that these are patients that are having potentially fatal events at a rate that would be quite concerning and would be called a very high-risk population if you'd enrolled them in a cardiovascular outcomes trial for whatever drug, just for a frame of reference. And certainly if it's closer to the 10 per 100 patient-years or 15 or 20 that we see in the Sentinel database, then that's obviously much more concerning given that it's a life-threatening event.

Ultimately, I think it's high, and what we're going to have to do, subsequently, is determine whether or not we think that risk outweighs any potential benefits that we might identify. So I'll stop there.

DR. LOW WANG: Thank you.

Dr. Nason?

DR. NASON: Martha Nason. I, first off, want to agree that I think there clearly is increased risk, and the clinical trial is probably the best case given the tight monitoring and the frequent contact. And it doesn't surprise me much that in the Sentinel data, it would be higher, though how much higher is the question.

I actually had a question about that Sentinel data, which is that slide that's 58 that you showed again, with the crude incidence rates per person-year, that does not include anyone without CKD as a baseline. Is there a line for stage 0 or no CKD?

DR. CHANG: No. We grouped people with eGFR greater than 60 into one group.

DR. NASON: Okay. So stage 1 and 2, that first row includes both who this would be indicated for, given that it's everybody over 60, and it also includes people who wouldn't really have CKD?

DR. CHANG: They would have an eGFR greater

than 90, but that's --

DR. NASON: Okay. So it's hard to have a comparison there.

Just the last thing I wanted to point out, which is something that a few people have mentioned in the public speaking, I think, is that I'm also very curious -- not that this is an answerable question with the data we have -- how the DKA risk might be different, now that we have changes in tact and so many more people having continuous glucose monitoring, for instance. I don't have a good sense of that. I don't know if anyone does, but whether that would shift it, how that might shift the rates, and what that really contributes as far as having more uncertainty about how this would apply now.

DR. LOW WANG: This is Cecilia Low Wang, and just a quick comment about that. Looking at DKA, the Sentinel data I believe goes all the way through 2024; is that correct? What were the dates of the Sentinel data? It was quite recent. We've had technology for several years, including the

automated insulin delivery systems for the last few years during that period that was looked at in the Sentinel data; 2013 to 2024. Thank you, Dr. Drake.

Okay. Mr. Tibbits?

MR. TIBBITS: Thank you. Paul Tibbits. Obviously, we're constrained to some degree by the construct of the question and the questions themselves. I certainly agree with most of what's been said in terms of the strict construct of the question in terms of what certainty do we have. I don't think we have a lot of certainty, but certainly there's evidence to suggest that people with CKD have a high risk of DKA, and people on this medication certainly seem to have a high risk of DKA.

With all that said, I do think talking about DKA as a life-threatening, or potentially life-threatening, risk I think is factual, but I think that also does not account for other benefits that we're not being asked about. So I would argue that the reduction of severe hypoglycemia is potentially life-saving, so severe hyperglycemia

and hypoglycemia are also potentially fatal events.

I think as we use words in these public discussions that we attach to certain risks, then we also need to think about what are the implications of certain benefits. We'll probably get to this in question 6, but what are the potential mitigation strategies for hypoglycemia that people with type 1 use versus potential mitigation strategies for an increased risk of DKA, as an example. Thank you.

DR. LOW WANG: Absolutely. I completely agree, and we'll get to that part of the discussion soon, I hope.

Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: For me, more patients entered real-world perspective. The incidence of DKA is important but, again -- I guess we'll get to this in question 6 again -- how you respond to it is probably the more important thing.

DR. LOW WANG: Great. Thank you.

Dr. Everett?

DR. EVERETT: I just wanted to add one quick

comment to my last one, which is that the incidence of DKA may differ by dose; that the question of 200- and 400-milligram dose doesn't come up in the FDA's questions, but at least based on slide 54, for me, FDA's package, there may be a difference by dose that may be worth considering as we talk about relative risks and benefits down the line.

DR. LOW WANG: Go ahead, Mr. Tibbits.

MR. TIBBITS: Paul Tibbits. Yes, I agree completely with Dr. Everett. I think I tried to articulate a question of similar nature to Lexicon earlier. But it does seem like there is somewhat of an increased risk of DKA for the higher dose and potentially not that much of a benefit of A1C. So I think some discussion or attention by the FDA and Lexicon, potentially, to what the different benefits and risks are of the different dosages I think is worth looking into. Thank you.

DR. LOW WANG: Any other comments from the panel?

(No response.)

DR. LOW WANG: Alright. This was a little

bit more difficult. I'll try to summarize. I think panel members mentioned that there's really substantial uncertainty in the magnitude of DKA risk in T1D with CKD. Part of this is because of the short duration of the trials. And, of course, we can't forget that DKA is a serious glycemic emergency; people die from it. Overall, the enrolled patients were at quite high risk for DKA with three or more events per hundred patient-years.

The Sentinel data showed a much higher rate of DKA than in the clinical trials, which might better reflect the real world, and the DKA risk with sotagliflozin in patients with T1D and CKD is really insufficiently characterized across the categories. The numbers are so small.

The available epidemiologic data suggests that CKD may be associated with increased risk for DKA. Patients with lower GFR categories, or lower GFR, are probably at higher baseline risk of DKA, and that risk of DKA might be increased with higher doses of sotagliflozin as well. And lastly, of

course, we have to balance this risk of DKA with other potential benefits, and we'll talk about that later.

Alright. I'm wondering if we have time to do one more question before the break, so let's go on to question number 4. This is also a discussion question.

Discuss your view of the scientific rationale justifying extrapolation of the demonstrated benefit of sotagliflozin to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in patients with type 2 diabetes, moderate to severe CKD, and other CV risk factors to patients with T1D and mild to moderate CKD.

Any questions about the wording of the question?

(No response.)

DR. LOW WANG: Alright. If there are none, we'll go ahead and take comments from the panel.

Go ahead, Dr. Drake.

DR. DRAKE: I note that the FDA has

underlined "demonstrated," and I think that if we focus on that word, then we're going to have pretty limited evidence, and we're really going to have to discuss rationale and really complete extrapolation, which really gets down to whether the short-term treatment that was done here versus the longer term treatment that was done in the type 2 study can be compared, and then, obviously, the significant differences that we discussed, as Dr. Everett really nicely brought out, between the baseline characteristics of the two groups.

So certainly, as a common mechanism of action for reducing glycemic control and perhaps non-glucose-centric approaches, certainly there could be some rationale. Again, I think that we have very limited data at this point to really hang our hat on.

DR. LOW WANG: Thank you.

Dr. Konstam?

DR. KONSTAM: It's very difficult to extrapolate from the SCORED data to this data set. There are numerous differences in the population:

type 1 versus type 2; worse CKD; more cardiovascular risk; older population as has been said. The other thing I just want to come back to and just state is I don't think the mechanisms are the same in type 1 and type 2. I don't know how to link the glycemic control to mortality. There's a linkage.

I don't think that's what's going on in type 2 because no other hypoglycemic agent has ever shown reduction in cardiovascular events, so there's something else there going on other than the glycemic control. In type 1, my sense is that the glycemic control is more dominant and is what is driving most of the adverse events. So again, it gives me another degree of uncertainty of whether I can extrapolate it.

I'll just mention, I was on a 2019 panel, and I have the same frustration now as I had then, which is here we are, and we're talking about it. There's been so much discussion and so much work into this. In our data set of trials, we don't have any direct information about clinical benefit

to the patient, and it's just very frustrating because there's no easy way to go from glycemic control and jump all the way to mortality benefit.

DR. LOW WANG: Thank you. I was also at that 2019 meeting, and I also am still frustrated. I agree with you. I think there are some similarities in the pathogenic factors for atherosclerotic cardiovascular disease, disease and heart failure, and type 2 and type 1 diabetes, hypertension, obesity. There are also significant differences like the lipid profile. The HDL is usually higher, triglycerides are usually lower in type 1, and then, of course, the degree and the causes of insulin resistance, presence and absence of hyperinsulinemia.

I don't think we can extrapolate the SCORED data to show that sotagliflozin has similar benefits to reduce those different endpoints in patients with T1D and mild to moderate CKD for those same reasons.

Dr. Everett?

DR. EVERETT: Brendan Everett. This is

really challenging because I think, as was outlined on the table earlier and as I suspect we all knew coming into this, while patients with type 1 diabetes and type 2 diabetes share diabetes broadly, the pathophysiology of the two conditions, of course, is very different. And as we heard from many people, including the sponsor, the age of onset is different. The duration of illness is different.

So there are an array of risk factors that relate to your likelihood of developing one of the outcomes of interest that's listed in this particular question, specifically cardiovascular death, hospitalization for heart failure, or an urgent heart failure visit, that are really more closely linked to having type 2 diabetes and moderate to severe CKD.

As some of our nephrology colleagues have pointed out, the Venn diagram between the population that we're talking about here with respect to their CKD and the one that was enrolled in SCORED, there's not complete overlap. And I

think we know from other trials -- and I may be wrong here -- one of the important ongoing questions in this field writ large is whether or not SGLT2 inhibitors, or SGLT inhibitors, in a primary prevention population that doesn't actually have established cardiovascular disease or heart failure, how effective they are at actually preventing those outcomes. That's a little bit what we're being asked here because while many of the patients with type 1 diabetes have some cardiovascular risk factors, we know from the table that was shown earlier that they don't have as many.

So it's not clear to me that the demonstrated benefit of sotagliflozin translates as easily as we'd like it to do, to patients with type 1 diabetes. On the other hand, I think we have to be careful of, shall we say, missing the forest for the trees here. But I'm having difficulty making the leap, basically, I guess I would say. Thank you.

DR. LOW WANG: Thanks.

Dr. Wang?

DR. WANG: Yes. Thomas Wang. I fully agree with the prior comments, and in particular I just want to reiterate that the fact that other medications in this class seem to have benefit with regard to heart failure, hospitalization, and cardiovascular death in both patients with and without diabetes, does reinforce the point that it's probably not all about the sugar, or it may not even be mostly about the sugar.

If you were to tell me a patient with type 1 diabetes, who shared similar risk factors to those patients that were enrolled in SCORED, and they had a similar level of cardiovascular risk factors, had a similar amount of CKD and the other things, that they would stand to benefit similarly, I would be inclined to believe that. But if you take someone just with type 1 diabetes and eGFR around 60, who lacks those other risk factors, I don't see where there's data to suggest that they would have similar benefit. I just think it's an unknown.

DR. LOW WANG: Thank you.

Dr. Newman?

DR. NEWMAN: Connie Newman. I just wanted to say that I agree with everyone who said we cannot extrapolate the data in type 2 diabetes in terms of cardiovascular events to the type 1 population, but I wonder whether the mechanism may be different, as has been suggested, in terms of reduction in cardiovascular disease in patients with type 2 diabetes, and I'm wondering about the reduction in blood pressure, whether that could contribute to the reduction in heart disease. But I don't think that's actually necessarily the question that's being asked.

DR. LOW WANG: Thank you.

Dr. Parsa?

DR. PARSA: Afshin Parsa. I guess I'm a little bit more comfortable extrapolating some of the benefits. I mean, we are in a different place than we were 5 years ago, and I keep going back to the point that if we're showing, both within sotagliflozin and also other SGLT2 inhibitors, benefits in both type 2 diabetics and

non-diabetics, to me, at some point, almost, you have to have a reason to think why it would apply to type 2s, non-diabetics with heart failure or CKD, and then not to type 1 diabetics, as opposed to showing that that benefit is there, because at some point, you're extrapolating here. So you look at the overwhelming evidence, and the overwhelming evidence is it's helping everyone that it's been tested in so far. So why would type 1 diabetes be different than everyone else, not just type 2ss, but there? So I'm comfortable doing that.

For me, it goes back to Dr. Wang's point and also depends on who's going to do it. If it's a 20 year old who doesn't have any atherosclerotic disease burdens, or heart failure, or anything else, there then, the absolute benefit would be less because of their underlying risk. And if they're a 50 year old, I'm fairly comfortable despite doing that there. But the overwhelming evidence I think is pretty high for it to be generalizable across CKD and CVD risk factors.

DR. LOW WANG: Dr. Konstam?

DR. KONSTAM: A quick response to that. I mean, I agree with a lot of what you said. In fact, I love this class of drugs. I wish they would put it in drinking water. I wish somebody would prescribe it for me. But it's the magnitude that we don't know. We have no direct evidence, so we're inferring from a lot of other stuff. I take your point, and I'd do the same thing, but what's the magnitude of it, and how does it counterbalance against the potentially fatal DKA? We don't have any insight into that, really.

DR. LOW WANG: Go ahead.

DR. PARSA: Afshin Parsa. The thing, too, is the magnitude of effect, when we look at all studies, has been fairly consistent, too, so that even gives me more comfort. If you look at magnitude of benefit around the CKD domain, or part there, it's pretty good. It's your underlying risk that will be your overall final benefit, but the magnitude of effect is remarkably consistent across different subgroups.

DR. LOW WANG: Cecilia Low Wang. I just

wanted to make a comment about that. In all of the SGLT2 inhibitor trials, patients with type 1 diabetes have been excluded, so we have no idea, actually, what the effects are. And I'm not sure why they're excluded from the SCORED trial. They could stand to benefit the most from that population. So I agree with Dr. Konstam that we just don't know what that is. We haven't studied them.

DR. PARSA: Afshin Parsa. But the point is the extrapolation. It goes back to if you're seeing it in everyone else, why not this group? Hoping to parse it, but it is applying to all people with -- if you have CKD, anyone with CKD, you give it, you see a benefit. Why would it be in everyone but not them?

DR. LOW WANG: Okay.

Dr. Onumah?

DR. ONUMAH: Barbara Onumah. As a practicing clinician, I take this into consideration, and I treat a lot of type 1 diabetes, and I think we have to be cautious when

we try to extrapolate data. To echo what Dr. Wang said before, if you have a person with type 1 diabetes who has some of the high cardiovascular risk factors -- a 70 year old who meets all the characteristics that we saw in the patient population for the SCORED trial -- it would make sense to put them on this drug, but the average 20 year old or 30 year old, probably not. So if we're going to extrapolate, we need a little bit more guidance and data to just generalize it and just extrapolate.

DR. LOW WANG: Thank you.

Mr. Tibbits?

MR. TIBBITS: Thank you. Paul Tibbits. I take to heart what is being said on both sides of me and across the table, but I think part of it is framing and part of it is what type of extrapolation are we thinking about. Certainly, I think Dr. Parse's point is, not surprising, one I would agree with more, which is unless we believe there's something medically, biologically, scientifically different about people with type 1

diabetes that would interfere with this mechanism of action across type 1 diabetes writ large, I think it's reasonable to assume that we would think these similar effects would occur in people with type 1 diabetes.

I think when you talk about clinical trials, there are multiple reasons why people with type 1 may not be included: potential complications, potential expenses, trying to find people with type 1. So there are a lot of reasons, I think, that have nothing to do with the mechanism of action. But with all that said, I do think we can't say that, very specifically, you can extrapolate the results from type 2 to specifically people with type 1 with moderate CKD. I don't think that's a one to one comparison. But within a pool of people with CKD, you will have some that do have some risk factors for heart failure and so forth.

So I think you can assume some people would have benefits that would extrapolate and some might not, but I think the bottom line is we don't know,

but I think how we frame it and how we think about benefits, I would align more with Dr. Parsa.

DR. LOW WANG: Thank you.

Go ahead, Dr. Konstam.

DR. KONSTAM: I just want to say, there have actually been negative trials with SGLT2 antagonists, and the one I'll cite is the EMPACT-MI trial, which is in post-MI patients with heart failure, and they showed no benefit in the outcomes, so I think you're on to something. I think it's true; there is something really special about this class of drugs, but I'm trying to be a little bit pure in terms of the way we think on the panel, and I'm not clear.

DR. LOW WANG: Okay. Just a reminder to speak close to the microphone.

Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: Prabir Roy-Chaudhury. I'm not going to be pure. I just want to support what Dr. Parsa said and what Mr. Tibbits said. I think the glycemic impact is, I think, a very minor part of it, so I think that they act in the absence

of diabetes, and I think that that really supports what Afshin said; that because of that, that's a baseline. They're going to work in type 1. I mean, would it be wonderful to have more data? Yes, absolutely, absolutely, but I do want to put my vote on that side. I think that's important.

DR. LOW WANG: Okay. We'll be super brief now.

Dr. Parsa?

DR. PARSA: I'll keep it short. I understand it's extrapolation, so I'm just putting it in that context. I'm fully aware we don't have all the hard data, and my point was really in terms of differences across when it's non-diabetics and diabetics, getting back to the point that it's probably some other mechanism, and I'm not aware of any data suggesting it would be different in type 1 diabetics, just like we don't have final proof, but definitely aware of the limitations.

DR. ROY-CHAUDHURY: Can I --

DR. LOW WANG: Dr. Roy-Chaudhury, go ahead.

DR. ROY-CHAUDHURY: I was going to make a

joke, actually. Many years ago, one of your colleagues, a cardiologist, actually said, in the early days of SGLT2 inhibitors, these are cardiac drugs with the side effect of lowering glucose.

DR. LOW WANG: Dr. Everett?

DR. EVERETT: Brendan Everett. I actually think that in many respects, we're all agreeing here, in the sense of the benefits of this class of medications, and to extrapolate those to sotagliflozin may or may not be fair given its extra inhibition of SGLT21. But the key is where the rubber meets the road is in the event rates because what you want to know is that the benefit that you're giving, and you're assuming there's going to be some kind of benefit, overwhelms or is more substantial than the risk.

We have some difficulty with the estimates of risk, but they're way better than any estimate on the hard cardiovascular outcomes that are listed on this slide in particular. We're going to talk about the other outcomes in a moment, but these outcomes, we just don't really have any data in

this population. And what we know is that these drugs work particularly well in people who are at high risk; kind of the sicker you are, the better you do with the drug.

Now, the patients enrolled in the type 1 diabetes have type 1 diabetes, which is an important and substantial lifetime illness, but they don't yet, many of them, have cardiovascular disease or really have a substantial burden of chronic kidney disease. So they're not sick in the way as patients enrolled in some of the registration trials or CVOTs for this class of drugs were. They don't have established CKD with a GFR of 30 to get into the study or established atherosclerotic cardiovascular disease.

So ultimately, what we're going to be asked to do in a moment is to compare the benefits to the risks. The benefits are listed on this slide as conjecture and extrapolation, and we're having trouble making the extrapolation. So we can agree that the medications have a substantial benefit for patients with heart failure, type 2 diabetes, and

chronic kidney disease, but not know how substantial that benefit would be in terms of the absolute risk reduction in this population; while we have a slightly better, although flawed, estimate of what the increased risk from an absolute standpoint is with the complications like DKA. So that's the rub. I think we agree; it's just a question of balancing what we know about the risks, the rates, basically.

DR. LOW WANG: Thank you. That is so true.

Dr. Shoben? Last comment.

DR. SHOBEN: Yes. I will be very quick, and I am not a physician. I just wanted to articulate for the record, this strict reading of the question is the extrapolation of the demonstrative benefit in these patients with type 2 diabetes and this moderate to severe CKD to patients with type 1 diabetes. So you switch the type of diabetes and mild to moderate CKD, so you've lessened the CKD, and that to me makes it hard to extrapolate and hard to estimate these different and actual benefits.

DR. LOW WANG: Alright. Thank you.

Just to summarize, I think we had a really robust discussion with lots of contrasting points that were made. I think people acknowledge that it's very challenging to extrapolate the SCORED data to the current population that the applicant is wanting the indication for. The mechanisms of CVD are different enough between type 2 and type 1 diabetes that we can't conclude that sotagliflozin has similar benefits to reduce CV death, hospitalization for heart failure, or urgent heart failure in patients with T1D and mild to moderate CKD.

The point was made that if patients without diabetes can benefit, why wouldn't we expect patients with T1D to benefit? Because it does appear to be a benefit that's independent of the glycemic effect. The main question really is that we have no idea about the magnitude, so we don't know what the absolute risk reduction is and how that balances with the risk of DKA. So patients with type 1 diabetes who have similar CV risk

factors to those patients who are enrolled in these trials might benefit from sotagliflozin, but we don't have those data and we need more.

So that brings us to the break. Let's go ahead and take 10 minutes -- actually maybe 7 minutes for the break and come back at 10 minutes to the hour.

(Whereupon, at 3:43 p.m., a recess was taken, and meeting resumed at 3:50 p.m.)

DR. LOW WANG: Welcome back. Let's move on to question number 5. This is also a discussion question. Question 5 is a discussion question. Discuss other potential benefits of sotagliflozin suggested by SCORED. Discuss your view of the scientific rationale justifying extrapolation of such potential benefits to patients with T1D and mild to moderate CKD.

Any questions about the wording of the question?

(No response.)

DR. LOW WANG: Alright. I'm not seeing any questions. Oh, go ahead.

Dr. Newman?

DR. NEWMAN: Connie Newman. I'm just wondering whether we are discussing only the evidence, the benefits in SCORED, or are we discussing the benefits in the TANDEM trial?

DR. LOW WANG: Could the FDA respond?

DR. ARCHDEACON: The next question has something where we talk about -- I think additional advantages is how we phrased it. So there, we're expecting a very broad conversation of everything, including the results in TANDEM, so hypoglycemia, blood pressure, weight loss. Here, we made the distinction between the heart failure indication that was awarded based on SCORED and the benefits that were not awarded but were nominally statistically significant, MACE and renal progression.

DR. LOW WANG: Great.

So now I'd like to open the discussion question for comment by panel members. Maybe I'll start.

I think that SCORED definitely showed the

primary endpoint. I think with the MACE endpoint, there wasn't adjustment for multiple comparisons, I think was one of the problems. As we were starting to look down at the different secondary endpoints, I think they stopped being able to show statistical significance because of that; so there's no adjustment. So I personally don't think there's an adequate rationale to justify extrapolating these potential benefits to patients with T1D and mild to moderate CKD based on our previous discussion.

In the subgroup analysis, I looked at the supplemental data for SCORED. There were no benefits seen for UACR less than 30, and of course there are lots of differences between the SCORED population and the TANDEM population.

Other panel members? Dr. Wang?

DR. WANG: Thomas Wang. I would have to agree that whatever my uncertainties and reservations are about the demonstrated benefits of sotagliflozin would exist for the potential benefits, and maybe even larger in terms of uncertainty. So overall, I would avoid

extrapolating too much from the SCORED secondary endpoint between populations.

DR. LOW WANG: Thank you.

Other comments?

(No response.)

DR. LOW WANG: I think the panel really wants to discuss the next question, but Dr. Everett?

DR. EVERETT: Brendan Everett. I'm struggling to try and find a table I wanted to look at in the FDA briefing document. I think the issue was the alpha spending rule with respect to the primary outcome. The SCORED trial showed a benefit but then ran up against cardiovascular death, where there was no benefit. So they had, at that point, spent their alpha and couldn't move any further down the subsequent, based on their testing rules.

I guess of the outcomes listed there -- and I was trying to find the table, but can't put my finger on it -- I think there's a potential to consider the renal outcomes, that there may be some potential translation there, albeit in patients

with type 1 diabetes, obviously, but who have kidney disease that's, I think, more advanced than this 60 to 89 bracket that we've discussed a little bit because that group, in some sense, is -- what did you call it, Dr. Seliger? It's not really even chronic kidney disease. What did you say?

(Seliger nods yes.)

DR. EVERETT: Yes, he nodded.

Anyway, I'll keep looking for the table, but there's the possibility that there may be some potential benefits that I'd be willing to translate, I guess is what I'm saying.

DR. LOW WANG: Alright. Thanks.

Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: Prabir Roy-Chaudhury. This is a question that I was wanting to ask earlier. I like the matched SCORED data, and I don't know whether we can go to the applicant, but is there data on UACR and eGFR comparing the matched SCORED? That's something we never got. From the SCORED data, they've taken out the 2,000 people who actually had the criteria of 45 to 60

or --

DR. LOW WANG: I think you're talking about the propensity score matching.

DR. ROY-CHAUDHURY: Yes. Do we have anything on UACRs and eGFRs?

DR. LOW WANG: Actually, I think the sponsor had -- did you have a comment that you could answer, respond to that point?

DR. GRANOWITZ: Craig Granowitz from Lexicon. I was addressing Dr. Everett's question, and I directed him to CO-62, which was the table that he had requested.

DR. LOW WANG: Okay. Alright. Terrific.

So, I don't know that we do.

Any other comments?

(No response.)

DR. LOW WANG: Alright. Well, I guess it will be quick to summarize, then, just a few comments. Overall, we think that we can't extrapolate these potential benefits of sotagliflozin from SCORED secondary endpoints, but there may be a potential benefit for the renal

outcomes, and potentially we could translate these benefits to patients with T1D with similar characteristics; so not so much the mild to moderate CKD population but probably patients with characteristics that are similar to the SCORED population, so moderate to severe with additional cardiovascular risk factors.

Any other comments about that?

(No response.)

DR. LOW WANG: Alright. Let's move to the last question. Discussion question number 6. I'll read the question.

Discuss the overall benefit-risk assessment for sotagliflozin as an adjunct to insulin to improve glycemic control in patients with T1D and GFR of 45 to less than 60 or a GFR of 60 or greater and UACR of 30 or greater. Address how to consider this increased risk of DKA relative to the benefit of an A1C improvement in the population proposed by the applicant. Discuss how you weigh other advantages of sotagliflozin in the benefit-risk assessment for the proposed indication.

Any questions about the wording of the question?

(No response.)

DR. LOW WANG: Okay. I don't see any, so I'd like to open up the discussion question for comment by panel members.

Mr. Tibbits?

MR. TIBBITS: Thank you. Paul Tibbits. I feel like maybe this question has a little bit been overcome by events. At least for me, I was very uncomfortable -- not very uncomfortable. I felt like we did not have enough information about the population as written, but with the applicant's presentation, I will say I feel like we have more information, and more information that makes me more comfortable about the benefit-risk ratio, particularly for the population between 60 and 90.

As I've said or suggested in earlier comments, I do think there are several things to think about as benefits. Again, knowing that the A1C reduction may be modest, I do still feel that an A1C reduction is worthwhile, particularly if you

listen to patients with type 1 diabetes. We have been told for many years that reducing A1C is sort of a gold standard for how to treat your diabetes, so I think we've imputed that there are certain clinical benefits to that; and I think there probably are, even though they're maybe not as well defined in these trials as we would like.

Certainly, I also believe, I think to an earlier discussion we were having, it is a little bit difficult to know how to translate a 20 percent reduction in hypoglycemic events into actual clinical benefit. With that said, taking into account my earlier comment that, essentially, any hypoglycemic event can very quickly spiral into a hospitalization or potentially fatal event, I would say that a 20 percent reduction in hypoglycemic events is fantastic. I think, overall, it would suggest that there's greater time in range.

Now, certainly there are certain endpoints that one can say you can coach a clinical trial participant to do X, Y, and Z. I think it's hard to coach someone to reduce your hypoglycemic events

when you come in for a check at part of your trial; so that one I think we can assume translates relatively well to increase time in range and certainly reduce the risk of a potentially fatal complication, to use a phrase that's been used before.

On the risk side, I think certainly we all agree, and it's very apparent, that DKA is an increased risk, but as many of the patients have discussed, I think the real question is not just DKA in a vacuum but what do patients have and what can they do to mitigate that risk? One of the things that I'm interested in -- and I think I'll probably talk a little bit about it in my closing remarks -- is a company like Lexicon, what can they do for patients who don't have access to a lot of these monitoring systems?

In the public comments that I read, one patient noted that their insurance company, as an example -- my working life is health insurance, and some health insurance companies won't cover ketone test strips or ketone monitors. So what is the

responsibility of a company like Lexicon to make sure that patients do have access to things like that, if that is part of the mitigation strategy?

Overall, though, I will say that certainly for at least one part of this triumvirate of patients that we're dividing into, there's one that I certainly feel quite comfortable saying that the benefits outweigh the risks for that group; sorry, the 60 to 90 to be clear. Thank you.

DR. LOW WANG: Great. Thank you.

Dr. Konstam?

DR. KONSTAM: Yes --

DR. ARCHDEACON: Can I just ask one clarifying question to Mr. Tibbits? For 60 to 90, and what about proteinuria?

MR. TIBBITS: I guess I'm more convinced by the FDA subgrouping that separating it into that subgroup probably makes the most sense without necessarily accounting for proteinuria.

DR. ARCHDEACON: Okay. Thank you.

DR. LOW WANG: Dr. Konstam?

DR. KONSTAM: I'm just thinking about the

situation, and it's kind of interesting because we in the clinical trial community and the patient community always would like to know can't we have a surrogate for mortality? Can't we have a surrogate for bad cardiovascular disease? And we have that in LDL cholesterol, and we have that in glycemic control, because there historically has been such clear correlation between glycemic control and reduction in microvascular disease, so let's just accept that. But here we're now up against a major adverse effect, so now quantitation becomes important.

So coupled with that on below 60 or with the albumin-creatinine ratio -- well, we don't know much about what happens with the albumin-creatinine ratio in this regard. But just taking the below 60, we're not sure even about the hypoglycemic effect of that. It seems less than the other groups.

I just think the problem is we're so uncertain about what is the magnitude of concern that we should have for DKA. We hear, and I'm ears

wide open, that there are ways of managing it, there are ways of mitigating it, but we actually didn't have a presentation on that. That would have been helpful. Look, here are the things we do. Here's the benefit. We have all these years that we've followed. Here's what we've achieved with that, so here's how concerned you should be. We don't have that in any quantitative way.

So the 60 to 90 group is an interesting add-on. It'd be nice to have been able to think about that ahead of time. So there I think the impact on glycemia is more clear, but it's sort of counter to what the sponsor started out to do to try to find a very high-risk population because the less kidney disease patients are going to have less risk, so I don't know how that works with regard, again, to the benefit-risk.

I just want to say, we were here in 2019, and we were stymied by the fact that we didn't actually have any clear evidence of clinical benefit. And maybe we've all been spoiled by being able to use glycemic control as a surrogate, so

we're not thinking about that. We're just thinking about glycemic control. But I think back then, if they had said, "Ok, look, we actually have to show some clinical benefit to weigh against whatever people believe about the DKA, so let's do that," I believe they could have done that.

I believe they could have studied their composite endpoints. They can use win ratio approaches. They can put health-related quality-of-life metrics at the end of a win ratio. They can put glycemic control at the end of a win ratio, and show then the other components of it are still going in the right direction. That'd be pretty credible to me. I'm just disappointed that here we are.

Let me just say one more thing. I've never been touched by the public comment the way I was today. I think the spectrum of people spoke so intelligently, with professionals and with people with the disease, and they're crying out for help. And it is being used without any guidance, so there should be guidance with it. I think emotionally, I

kind of feel, look, this probably is right. SGLT2 antagonists do such good, it's probably going to work here. So I would say come out of this, and get back together and say, how can we get over the hump of actually convincing a panel that from a scientific basis, this is a benefit to patients?

DR. LOW WANG: Thank you.

Dr. Wang?

DR. WANG: Yes. Thomas Wang. Also just to echo some of the prior comments, thinking about going back to 2019 with the original request and the original advisory panel, there was a struggle to articulate the balance of benefits versus risks, and as a result of that, FDA in the CRL -- and I'm just reading from the briefing document -- wrote in the path forward section the suggestion of identifying a group of patients for whom the benefit of sotagliflozin may outweigh the risks, and prospectively study these patients.

For me, that's kind of what it comes down to. I don't see where the new prospective data are here. The sponsor deserves credit for doing other

prospective studies like the SCORED study and SOLOIST, but I think those populations were sufficiently different that I don't count those as answering this request. And I think that's partly why we are where we are today, which is I think everyone in the panel, to Dr. Konstam's point, would like to be able to recommend a new therapy for patients with type 1 diabetes because there's certainly unmet clinical need, but there's so much uncertainty on the benefit side of the equation, and on the risk side of the equation because we don't have new prospective data, and we're relying on these post hoc analyses, that it's just hard, at least for me, to strongly recommend moving forward in this way.

DR. LOW WANG: Thanks.

Dr. Irony?

DR. IRONY: Yes, thank you. Dr. Irony. My point here is very nuanced, in the absence of very robust and conclusive data to maybe introduce the discussion about the 200- versus 400-milligram dose, where we have a flat response in terms of

glycemic response, hemoglobin A1C, change from baseline, but there is an increase in risk or in DKA with a higher dose. So my point here is, is there a balance here where we can see if there is some overall positive benefit-risk here with a lower dose versus a higher dose? And I don't know the answer to this, but I think it's a point that we need to consider here.

DR. LOW WANG: Thank you.

Dr. Roy-Chaudhury?

DR. ROY-CHAUDHURY: Thank you. Prabir Roy-Chaudhury. I'm going to start off by saying that from the time I started reading the documents till now, I think I've changed my mind about 10 times. I guess my comments are going to be -- and I think my comments will show the equipoise in this -- to start off by saying that if you live just in a small bubble with the data that's in front of you, and that's sometimes easier, then I think we're in a setting where we've got a serious side effect that you could die from, and you've got some benefit in your control of

glycemia, but you don't really know what that's going to translate into, and maybe you shouldn't be going down the pathway with this drug.

But then if you go to a much bigger bubble, I would say much more real world, I start off by saying that it's so frustrating that the data in terms of clinical outcomes isn't there. But then when you're living in this much larger, real-world bubble, you have to bring in things like what are all the non-glycemic effects that are associated with this agent? And you have to bring in, I think, all the things that we heard from patients about being more patient-centered.

Then I think if you live in this larger bubble, and then you combine it with, let's say, a REMS program with teeth -- in other words, all the stuff that we heard about STICH and STOP -- then maybe in this larger bubble, there is perhaps a positive answer to what we're saying, and maybe there is a population, and maybe it is that 60 to 90 population where there could be benefit in using it.

I think that one of the points that was made, and I think Dr. Konstam alluded to it as well, is it's being used in 2.6 percent. It's gone from 0.1 to 2.6 percent; 34,000 people, apparently. And I've heard this when talking to people in our institution, but everyone's using it in different ways. Maybe it would be good if we could use this with certain strict guidelines, and maybe that's a plus for the whole community.

Then I just want to end by saying that the benefit in using this could actually come in vulnerable populations who may not be able to control their blood sugar that well. There's the obvious, of course, that these same populations may be at greatest risk of the DKAs. So if there is a risk mitigation strategy, it's really important. Paul, you brought that up. I think that's a really good point, that it needs to extend to everybody who would use it, particularly vulnerable populations.

So I guess, putting it all together, I think maybe it is time that we identify a patient

population where we can actually use this agent in a type 1 diabetic population that will, I think, move the needle forward.

DR. LOW WANG: Thank you.

Dr. Yanoff?

DR. YANOFF: Thank you for all the helpful comments so far. I just want to remind you the voting question is where you have the opportunity to make a recommendation or provide a binary opinion. What we're really interested in, in this question, is how you're weighing the benefits of A1C reduction in this particular population and the other advantages of sotagliflozin, such as the hypoglycemia against the risk of DKA, how you're balancing those, and how much uncertainty you have in balancing those. The next question, we very much appreciate the decision, the recommendation, and where you're recommending FDA move from here.

DR. LOW WANG: Thanks.

I just wanted to mention -- Cecilia Low Wang -- we see this small reduction in A1C, but it seems to be attenuated for those patients with a

GFR of less than 60. I think the potential advantages of the change in body weight, that's really significant. We don't really have a whole lot for our patients, and that effect on decrease in body weight appears to be consistent across GFR categories.

I think the reduction in the rate of level 2 hypoglycemia, the increased time in range, I think that's all really important for patient-centered outcomes, but we really don't have the data for that. We heard a lot during the open public hearing that was really compelling, but we need some information and some data from the trials as well. Overall, I don't feel that these potential benefits have been demonstrated to outweigh the increased exposure-adjusted incidence rate of DKA with CKD.

Those are my concerns, and now I'd like to move to Dr. Newman.

DR. NEWMAN: Connie Newman. Thank you. I agree with what you said, Dr. Low Wang. I've been thinking about this for weeks, whenever I got the

documents, how I don't see a definitive benefit in the population with the GFR below 60, but I do see a benefit in terms of reduction in A1C, a modest effect, maybe 0.3. In the other population mentioned here, which would be GFR over 60 and a urinary albumin-creatinine ratio of 30 milligrams per gram or greater, what I'm struggling with is how to balance that against this real risk of DKA, and I don't actually know how that can be done without perhaps education of a population of the patients with access to the new equipment that they can use to check ketones.

So I just don't think, right now, in my mind, it's balanced positively, but there are other concerns that were mentioned, other good points like reduction of hypoglycemia and decrease in body weight of a small amount, which might not lead to a 5 percent reduction, which is what is needed to improve the comorbidities of obesity. But also, there is a 2 to 3 millimeter mercury reduction in blood pressure, which could translate to an improvement in cardiovascular events, but that

hasn't been proven, so I'm still struggling with trying to balance this. Thank you.

DR. LOW WANG: Thank you.

Dr. Everett?

DR. EVERETT: Thanks. Brendan Everett. So this is the meat of the matter, and it's really hard. It's pretty clear to me, just from reading the briefing books but also from hearing patients during the public comment period, that the reduction in hypoglycemia is a really important benefit. It allows patients to have better control of their A1C without risking further episodes of hypoglycemia, and I think that's a really important benefit that perhaps we haven't discussed much.

I think the reductions in blood pressure and weight are also important given that both of those risk factors can increase the likelihood of developing kidney disease, or for that matter, cardiovascular disease. The A1C benefit is modest, I would say, and I think the challenge is that we're betwixt and between here. We want outcome data that address the likelihood of kidney disease

progression in people with an eGFR less than 60 because then we have something, and we know how many patients end up on dialysis, for example. We can weigh that against the number of people who have DKA, and that is a calculus that maybe is a little bit easier to understand or intuit.

But of course, we can't do that, and the outcome, or the indication, is A1C reduction. So it's one of those most storied, the indications in the FDA, but it's still hard to weigh that, I think, against something like DKA. Maybe this is because -- what do they say? You're afraid of things you don't understand or don't know much about. Well, that's me as a cardiologist to DKA, so I worry about it. I can remember taking care of patients when I was a resident, and they worried me when they were sick.

So I think that concern about that illness, or that adverse effect, has made an impression on me. So it's really difficult, I think, to balance those benefits, which I think are real, and the risk of this other outcome, which, again, strikes

fear in my heart, but which I think is important nonetheless.

DR. LOW WANG: Thanks.

Dr. Shoben?

DR. SHOBEN: Abby Shoben. I was just going to comment to say that some of the other advantages that come up qualitatively from the the open public hearing about not having to worry as much about your sugars and your diabetes and stuff didn't really seem fully captured to me. You can get at it from the hypoglycemia, but I would really like to see a better quality-of-life potential outcome measure. Thanks.

DR. LOW WANG: Thanks.

Dr. Drake?

DR. DRAKE: Matthew Drake. I just wanted to actually get back to the question that was actually asked by the FDA A little bit here. I think we are going to have a hard time finding data related to type 1 diabetes and eGFR greater than 45 or in the 45 to 60 range, but they're really not asking about the 60 to 90 range or greater than 60; they're

asking specifically about greater than 60 and the renal protein losses of greater than 30 milligrams per gram. If we look back, when they combine the data from the 309, 310, and 312, that was really only about -- well, 30 to 300 was only 10 percent of the entire patient population that was studied, and then greater than 300 was another 3 percent. So in total, it's really 13 percent of the entire population that we're talking about.

So I just feel like we're a little bit handcuffed here, specifically with this question, and I'm not sure we really actually address the question that was actually asked by the FDA, specifically. And maybe that's correct or not, but maybe the FDA could weigh in because they give a very, very specific question, and we've really much more generalized with the eGFR as opposed to really not spending much time on the renal protein losses.

DR. LOW WANG: Does the FDA want to respond to that?

DR. ARCHDEACON: Sure, and we'll see when we get to the voting question. I think the reason why

we picked this particular population is it is what the applicant proposed, but we will invite you, after you vote on what the applicant proposed, to talk about any other populations that you think are more clear-cut. If there is a clear-cut population, I think we at FDA should be in listening mode as opposed to saying what we think, but I'll risk saying that it does seem to us that proteinuria is relevant to what someone's absolute risk is. So that's why we've also made sure to introduce that into the question.

DR. LOW WANG: Thanks.

Dr. Konstam?

DR. KONSTAM: Yes. To try to address Dr. Yanoff, how do you compare DKA to A1C, well, my first response to that is one is a clinical event and the other is a blood test. Okay. It's a very meaningful blood test. We know it serves as a surrogate, but at the end of the day, it's a blood test. And five years ago, I asked, give me some help in translating the glycemic control that you achieve into its impact on the patient.

So if I know that there's, whatever it is, X percent reduction in A1C, how much reduction in retinopathy can I expect from that? How much prevention of kidney disease can I expect from that in some kind of quantitative way? I think when you start throwing the other things in, which are really relevant -- the hypoglycemic events, the weight loss -- okay, build a composite primary endpoint and do a clinical trial. Those are all real things, but they were never really designed as efficacy P endpoints or pieces of an endpoint.

So it's a real struggle to work with these data from that regard, and if the company's going to go -- I'm not going to make any more recommendations until the next question.

DR. LOW WANG: Great.

Dr. Wang?

DR. WANG: Thomas Wang. Just very quickly to address the issue of other advantages, blood pressure has been brought up a couple times, and it did look like there was a couple millimeter mercury reduction in blood pressure. I would say, though,

that while that's clearly beneficial if you have hypertension in diabetes, it's not so clear if you have a normal blood pressure that reducing blood pressure has additional benefit. But in the ACCORD BP trial, there was no additional benefit from intensive blood pressure lowering, and it looked, if I recall correctly, in the TANDEM population, that the prevalence of hypertension wasn't all that high and looked like only about 30 or 40 percent of the individuals were on an ACE inhibitor, which we know is good for a lot of things in diabetes and CKD. So again, while there may be a real reduction in blood pressure, I'm not sure that that would have clinical benefit across this population.

DR. LOW WANG: Great, thanks.

And Dr. Parsa?

DR. PARSA: Afshin Parsa. Well, like many here, I've been struggling a lot with this, and similar to Roy-Chaudhury, I keep changing my mind because, well, as we all know, the data is really insufficient to have a clear idea of both the magnitude of the real risk in the real world, which

I'm still very concerned about, and I think I will go more with the Sentinel data than the clinical trial data.

Of course, the benefit, again, can be quite high but, to me, it really becomes, given that there is a real known risk, at least the benefit should be really focused on a subgroup where there's the most evidence -- even though none of it's perfect here because, as we discussed, it's different populations -- of poor to bad outcomes.

The proteinuria I think was a great thing that was brought in because, consistently, both for cardiovascular disease outcomes and for renal outcomes, proteinuria really stratifies risk like hardly any other biomarkers have done to date, and fairly consistent. If your proteinuria is high, you do poorly whether it's in trials, whether in the PERL data. Even if you had high A1C and no proteinuria, your risk wasn't elevated, and then if you have proteinuria, it becomes more, and then that's compounded with the A1C, and that's not just PERL, but consistently, we've seen that data there.

So to me, I think, at a minimum, one would have to make sure that the risk is high enough to even consider that.

Now, given the uncertainties, it's easy to weigh away, but I was also a little bit affected by all the type 1 diabetes patients and the associations in terms of wanting therapeutic options, and then realizing if we get out of assessing the science and the clinical data back to a bigger bubble, as Prabir said before, the therapeutic options and some of these things, they're really all gray zones. That's how we operate in clinic. And maybe some of this needs to be left between a patient and a doctor but, again, with us setting boundaries, because if we want to try to group this into a clearly defined group, we clearly don't have the data; then it's easier to just stop because it's not there.

So I think the high-risk profile definition of that, or determining that, with some proteinuria, or even more than that, would be an essential component in my view.

DR. LOW WANG: Thank you.

Mr. Tibbits?

MR. TIBBITS: So I'm going to pose something, and I guess it's a little bit theoretical. It's less data and more theoretical/moral. I think we've been looking at a lot of numbers, but I think the other question, which I will admit is virtually impossible to answer, is what is the benefit-risk of not having this drug available to people with type 1 diabetes?

I think it's not just a question of what do the trials look like, but I think the question also is, if we were to go down path A and it was available, what are those benefit-risks? And then if we go down path B, which is the status quo, what are those benefits and risks? So is there a potential population that would benefit from path A, but we don't let them go down path B, so therefore, they have early death and they have other complications? I think that's maybe a not calculable number, but I think it's something that we need to think about.

I think the other thing that I would say is we all seem to generally agree that, to use Dr. Everett's phrasing, "there's a paucity of data," which I think is frustrating for all of us. I don't love rewarding a company that has not done a great trial design, but with that said, I also think if we know the data that we want, or we know what additional data would help us, I think the other consideration to weigh these risks and benefits is, is the better approach, however you want to define "better," to send it back to the sponsor and say give us more data, or is it to send it into the real world and do something like Dr. Roy-Chaudhury said, and implement some sort of REMS strategy that would potentially give us additional data in the real world? Which I would argue, then has the advantage of being real-world data versus tightly controlled clinical trial data. Thank you.

DR. LOW WANG: Great. Thanks.

So if there are no more comments -- those were really great points that were made -- let me

try to summarize. I think that, overall, there's evidence for small but significant A1C lowering across the GFR categories. It looks like that may be a little bit more modest or attenuated with those in the GFR less than 60 category. That 20 percent reduction in hypoglycemia that's estimated appears to be a significant benefit, especially if it translates to improve time in range, but we really need more evidence for patient-reported outcomes.

Reduction in body weight is important. There's also this reduction in systolic blood pressure but, really, a reduction in systolic blood pressure doesn't translate to clinical outcomes or a clinical benefit if a patient is not hypertensive.

There was the point brought up about evidence for effectiveness of the DKA risk mitigation strategies. There was still a significant event rate for DKA in the clinical trials, and there is also the question of what will the applicant do about patients without access to

all of the ketone monitoring support that's needed in order to reduce the risk of DKA. There was a point brought up about whether a lower dose might change the benefit-risk balance; and then, overall, it's a struggle to conclude anything from the available data.

There's mention about being disappointed about where we are. The subgroup of patients with type 1 diabetes who might benefit the most were not prospectively studied, and we don't have the information to calculate a win ratio.

Any other additions to that or modifications?

(No response.)

DR. LOW WANG: Alright.

Well, I think we will now proceed to question 7, which is a voting question. We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're

unsure of the vote or you want to change the vote, you can press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen, and Joyce Frimpong will then read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. Please also state the reason why you voted as you did. We'll continue in the same manner until all questions have been answered or discussed.

Question number 7 is the voting question. Do the available data demonstrate that the benefits of sotagliflozin outweigh the risks for the indication of improved glycemic control in a population of patients with T1D and eGFR of 45 or greater to less than 60 or GFR of 60 or greater and UACR of 30 or greater?

If yes, provide your rationale and suggest specific risk mitigation approaches. If no, do the

data demonstrate that the benefits outweigh the risks for the indication of improved glycemic control for another population of patients with T1D and CKD defined by different GFR and/or UACR categories? Explain and clarify the population in which the benefits of improved glycemic control outweigh the risks, if any.

Any questions about that voting question?

Go ahead, Mr. Tibbits.

MR. TIBBITS: Thank you. So in terms of this "or," does the "or" mean -- let's assume that this was the indication question. Does the "or" mean that a physician would look at this and say, if you fit into category A or category B, then you're eligible, or are we as members able to say, yes, but we only agree with one of these categories?

DR. ARCHDEACON: So the indication statement proposed means that if you fit into either, then you fit, but we certainly encourage you, for the second-half of this question, if you felt that only one of those you agreed with, then you can clarify

that. I know that people may be concerned about, well, I want to vote yes, but I'm saying no but yes. Please be assured that I will be taking very careful notes, and if there is consensus on some other population, we are not beholden to numbers here. We are listening to the conversation.

DR. LOW WANG: Alright. Any other questions?

(No response.)

DR. LOW WANG: Okay. If there are no further questions or comments concerning the wording of the question, we'll start the voting process.

Oh. Go ahead.

DR. PARSA: Afshin Parsa. Just to clarify, if we agree to one and not the other, we can still vote yes, and then give a disclaimer, or the other way around?

DR. ARCHDEACON: I'm happy to have you do it either way. If you want to vote yes but explain that no, I actually meant no, but whatever; or you want to vote no but explain yes, that's what I mean

when I'm saying I will be listening to what you say. The numbers matter, but what really matters is your explanation.

DR. LOW WANG: Alright. Are we set?

(No response.)

DR. LOW WANG: Okay. Now, we will begin the voting process. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly, and after you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change it, please press the corresponding button again before the vote is closed.

(Voting.)

DR. FRIMPONG: Joyce Frimpong, Designated Federal Officer. There are 3 yeses, 11 noes, and zero abstains.

DR. LOW WANG: Okay. Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and also please state the reason why you voted as you did

into the record. We'll start with Dr. Roy-Chaudhury.

DR. ROY-CHAUDHURY: I'm glad, Patrick, you said that you're listening because --

DR. LOW WANG: Please state your name and your vote.

DR. ROY-CHAUDHURY: Oh, sorry. Yes. Prabir Roy-Chaudhury. Thank you.

DR. LOW WANG: And did you vote yes or no?

DR. ROY-CHAUDHURY: So I voted a yes. Can I provide the rationale? Yes. I voted yes because, as I'd spoken earlier, I think it's important to live in a big bubble, and it's important to have risks. And I do believe that risk mitigation strategies will work. But I do want to say that I voted yes, really -- if I had to give a group, I voted yes for the 60 to 90 group with a UACR of greater than 30. That's the group that I think needs to be targeted. I think that when we target that group, it's really important to be very, very focused on a REMS with teeth, if you will.

DR. LOW WANG: Alright. Thank you.

Betsy Chrischilles?

DR. CHRISCHILLES: Yes. Betsy Chrischilles. So I voted no, but I wanted to vote yes. But I didn't vote yes because of the very specific nature of the question, and the very specific population, and the small numbers of individuals that were represented, and the uncertainty that that left me with. I would have felt differently if the question were about the 60 to 90 category.

Then in terms of the balance of benefit and risk, it is difficult to not have new prospective data. We do have some new data in the observational world that we didn't talk about today, where we have some information from off-label use of this class in type 1 diabetes, which is of interest for future monitoring, I think, and I would like to see that aggressive monitoring of the experience, if this could be approved and would be important.

DR. LOW WANG: Thank you.

Dr. Newman?

DR. NEWMAN: Connie Newman. I voted no

because I felt that there was an uncertainty about the benefit-risk. I felt from the data we have seen, it seemed unfavorable to me, and we really had very few patients in these categories to make a decision.

Do you want me to answer another question about what group, what population it might be beneficial in?

DR. LOW WANG: Yes.

DR. NEWMAN: Oh, ok. I was thinking that the group with GFR between 60 and 90 might be a population that would have a greater benefit than risk. They have less of a risk of kidney disease, and I would prefer to see more data in that population before I can make a decision about benefit-risk. Thank you.

DR. LOW WANG: Thank you.

Dr. Onumah?

DR. ONUMAH: Barbara Onumah. I voted yes, but I was very conflicted, and I think my yes is specific to the population with eGFR between 60 and 90. I think this overall benefit in terms

of A1C reduction is quite modest, as we've already discussed, and there are some non-glycemic effects that may be very beneficial. We know there's a paucity of data as it pertains to these benefits; however, persons with type 1 diabetes have very limited treatment options, and it's already happening in the community. There are other SGLT2 inhibitors that are being used without any guidance.

So my vote of a yes comes with the caution that this should be used with strict risk mitigation instructions for patients and providers. And if we can do that, at least if this is going to be used and there's a risk of DKA, it can be done in a structured manner.

DR. ARCHDEACON: If I can just ask the people who have clarified, I think I've gleaned from what people have said so far. The answers can be yes, no, but I recommend this alternative population, or no, I don't think the data is there for any population. And what I've understood was Dr. Roy-Chaudhury was a yes overall.

Dr. Chrischilles, I think you were a no, but yes for 60 to 90 and UACR greater than 30. I think, Dr. Newman, you were a no overall, even though you thought that it was more encouraging for the 60 to 90. Did I glean that correctly?

(No audible response.)

DR. ARCHDEACON: And Dr. Onumah, if you could just be a little bit more clear for me. Again, if you could just bottom-line it for me at the end; is there any subgroup that you are recommending?

DR. ONUMAH: Yes, and for persons with eGFR between 60 and 90.

DR. DRAKE: Matthew Drake. I voted no, and it was really very specific to this question. The way the question was worded, specifically, I just don't think we have the data for that. That said, I would be supportive of this for the group in the 60 to 90 category. I think that the data, as presented, has the potential to help that group, and maybe the greater than 30 milligrams per gram is the best population, but I just don't think we

have that data yet. The worse the kidney function is, likely, if we extrapolate to other SGLT inhibitors, this would be a group that would be particularly benefited, likely, on average. But again, I just don't think we have that for here.

So I voted no, but I would say yes to the 60 to 90, and I would like to see a little bit more data, but that's where it is. I certainly do have some concerns about diabetic ketoacidosis. That's a real concern. But that said, these can be reasoned conversations had between clinicians and patients who live with this potential on an everyday basis, be it hypoglycemia or diabetic ketoacidosis. Hypoglycemia is a real risk and has immediate consequences as well for these patients. Thank you.

DR. ARCHDEACON: Thank you. And my last ask is for people not to forget, if they are saying yes to any group, if you have concrete advice about risk mitigation, things that must be as part of the risk mitigation.

DR. DRAKE: I would love for these patients

to have a CGM, but it's hard for me to make that. I think a lot of these patients do and would, but not necessarily all would have access to that.

DR. ARCHDEACON: Thank you.

DR. LOW WANG: My name is Cecilia Low Wang, and I voted no. I actually didn't see any data that demonstrated that the benefits outweigh the risks for this indication for another population of patients with type 1 and CKD. I wasn't convinced by the data for the 60 to less than 90 subgroup. The numbers were incredibly small. I really feel like we need a prospective trial.

I have a really hard time voting to approve a drug when there's so little relevant data, and I very much want an adjunctive drug for my patients with type 1. I just don't feel that it would fulfill my obligations to vote to approve something with so little supportive data. I feel like it does my patients a disservice. It's been argued that the FDA should approve this class of drugs since it's already being used off label anyway, but I really don't know that that's an adequate

argument. I think we actually need some good data to support approval.

DR. WANG: Thomas Wang. I voted no, and I also was not ready to say that for any patient population, I was convinced that the benefits outweighed the risks, or at least I should say I was convinced that we have the data to demonstrate the benefits outweighed the risks.

I think the sponsor presentations and the open public comment period really did a nice job of outlining the unmet need. I truly believe there is an unmet need, and there is potential benefit of the drug in this context, but given what we have as data in this predefined subgroup, while there may be theoretical reason to believe there's greater benefit, we haven't excluded greater risk either.

So I think, ultimately, we need a little bit more data, and that doesn't necessarily mean you need to do another cardiovascular outcomes trial in type 1 diabetics. I think that with the availability of cardiorenal endpoints, there may be other ways of getting this information without the

same magnitude of trial, which I know is challenging in this patient population, but that ultimately was the rationale for my vote.

DR. EVERETT: Brendan Everett. I voted no. I think it's challenging because this group of patients needs another therapy, and I think the unmet need for A1C control and just improvement in quality of life is substantial. I was, I guess, left a little bit with the sense that we were revisiting the conversation we had five years ago without huge amounts of new data. We have the SCORED trial, but in the process of looking at it carefully, felt like it's applicability was modest at best.

Then I recall thinking, whatever, five years ago, this was potentially doable if we had a really creative risk mitigation strategy, and that wasn't really part of the conversation at all today, except to suggest something now at this point when all is said and done. So I think that's potentially a missed opportunity to really create, and investigate, and test risk mitigation

strategies for DKA specifically. I think we can see a little bit that just being in a randomized trial was a risk mitigation trial strategy as opposed to just being in the general population.

Also, I hear my colleagues here talking about being in a bubble that's too small or too large. I think we're focused specifically on the indication of improved glycemic control, period; and I think there's a lot of rationale for thinking about this class of medications writ large for improvement in kidney outcomes in this population of patients.

So you could think of that as an unmet need, and I think we all wished that we had those data. We don't because there aren't any new data, and we decided that the SCORED data were modestly applicable. But then you think about is that an unmet medical need, and it's not really because they're actually two drugs approved for that population for the improvement in kidney function or risk reduction of chronic kidney disease outcomes in all patients with chronic kidney

disease, including those with type 1 diabetes.

So ultimately, it was hard to say that much had changed from 2019, and I struggled with this because on some level, patients, particularly the patients who showed up and spoke in the open session, have the capability to understand these risks, and to accept those as their own, in conjunction with their physicians, of course, and manage those risks. That's a little bit of a different population, I think, than you're necessarily going to see who gets the drug, if it's available and seen as a labeled indication for glycemic control in type 1 diabetes. Thanks.

DR. KONSTAM: Hi there. Marv Konstam. I voted no. I want to say, first, that I was really moved by the public comment, and as somebody else pointed out, there clearly is an unmet need. People are suffering and physicians see that they need more, so I get it. The question is, does this body of data show us what they need? And I can't get from here to there.

Now, why is that? Well, first of all, I'm

uncertain about the risk side. I'm queasy about accepting what the trial shows is the actual real-world risk of DKA. On top of that, I believe that risk mitigation can work for this; I just haven't been shown it. It hasn't been clear to me what exactly is planned. Did they attempt to implement the risk mitigation in this trial population? Can they do that? Can they take the patients who are getting it off label -- would that be ethical? -- and do a registry that includes risk mitigation in them to show that it's working? I don't know if that's doable, but maybe. So that's the risk side that I'm queasy on.

I can't find a population that works for me. The starting point was to find a population that's at high enough risk that it will allow us, in our minds, to shift the risk-benefit ratio. Well, these populations don't really tell me that much. These populations are higher risk populations; therefore, they have a greater opportunity for absolute risk reduction, for greater absolute risk reduction. But I don't know what that absolute

risk reduction is, and I don't know how to figure it out.

Let me say the body of information here is enormous. There's a lot of really interesting good stuff. We can all find a number of things here that say that should be on the benefits side, and that should be on the benefits side, but there's no way of quantifying that. So I would like to see, ok, we've got enough here that we can now construct a clinical trial to show you some clinical benefit, and let you calculate quantitatively, pull it together and say, if you assume this/that, here's what the quantified risk-benefit ratio would look like.

Now, if nobody wants to do another clinical trial, I don't know how you fix it. The only thing I can think of is to do modeling around the data that you have. Make certain assumptions about what the degree of glycemic control shown here would translate into, into some clinical benefit based on other information that we need, correlating those two things happening, and say, ok, here's our best

guess at what that means clinically.

Can you do that? Can you incorporate things like hypoglycemic events and weight loss? If I were doing a trial, I'd like to say maybe I can build those into a composite primary endpoint. If you're not going to do another trial, I don't know. How do you pull that together? How do you figure out -- how do you weigh that benefit against the risk of a fatal DKA event? There's no way for me to quantify those things here, so that's where I am.

MR. TIBBITS: Paul Tibbits. I voted yes with an asterisk of sorts. I think it won't surprise anyone to know that I'm less comfortable with the 45 to 60 group. I voted yes largely for the 60 to 90 group, and I could be convinced to limit it further to the over 30 group creatinine ratio.

I guess I'll take a step back and say, I think from many corners, the FDA is criticized for erring too much on the side of patient safety and conservatism, which I don't think is a fair

criticism. I think it's an important issue, and I think, certainly, overall, the FDA does a really good job, I think, of taking into account exactly what we're talking about today, benefits versus risks.

I think what makes it difficult for me in a disease like type 1 diabetes is that people with type 1 diabetes are so different from each other in terms of responsiveness to insulin, responsiveness to exercise, responsiveness to diet, so it's a little bit of an art, a little bit of a science, and a little bit of luck. So to try to say, overall, we're going to make a decision for however millions of people we are and take that conversation away from the doctor and patient is a real struggle for me. So I do feel, in this case, there's enough data to say, for this limited population, we should push this conversation out to the doctor and the individual patient.

I think anyone who heard my participation at the last EMDAC back in May knows that I'm not a rah-rah patient advocate; that everything that

comes down the pipeline for type 1 should be approved. So for what it's worth, to me, it means something, and I think there's enough here for at least a group of the population. With that said, I will again repeat that I don't think the sponsor should be let off the hook and think that they have enough data that makes this a slam-dunk, as they can tell. I do think risk mitigation would include figuring out a way to provide ketone monitoring systems/supplies to patients that have no access.

I think it would also include -- and I don't know what levers the FDA has exactly -- some data collection to improve the data that we have. So whether it's doing matched controls with the HRs, or whatever it is, there are probably more erudite people than me that can figure that out. But even a risk mitigation strategy, I think, without data is only marginally helpful. So, for me, part of the risk mitigation would have to be demonstrated, ideally a clinical benefit of the sort that we were talking about. Thank you.

DR. NASON: My name is Martha Nason. I

voted no. I think most of what I have to say has been said by some around the table, but I will rehash a little bit anyway just to get my own opinions out there.

I think there clearly is a clear need, and the public speakers emphasized how much of a clear need there is, but these analyses are ad hoc. They require too much extrapolation and generalization, and, to me, there's too much uncertainty about potentially fatal consequences and not enough new information or data to change the decision from the one that this committee made -- well, the recommendation that this committee made in 2019.

I think we heard people mention that type 1 diabetics are often excluded from studies, and I think they deserve to be studied, and I think they deserve to have these questions answered in those people and not extrapolated from type 2 diabetics and say, well, maybe it's close enough. I think really having data that is known to be relevant on type 1 diabetes as far as risk-benefit ratio and cardiovascular effects is important and is

respectful as opposed to just continuing not to study those things and just making assumptions.

I do hope there will be eventually a new prospective clinical trial. There are clearly lots of motivating data here. I don't know if there will be, but if there is, like this has been said, I think it would be really important to think carefully about not only the proposed population, really specific risk mitigation schemes, but how the overall clinical benefit is captured as far as whether that includes cardiovascular, and kidney, and diabetes outcomes all put together in some kind of way.

DR. SHOBEN: I'm Abby Shoben. I voted no, and I also don't think there's any subpopulation in which the benefits outweigh the risks. I think the only comment I have that hasn't been said is the idea that I would really like to see some more current data on the potential risk mitigation strategies in a more controlled environment; so not from a send it out into the world maybe with the REMS, and see what happens, but like an actual

controlled environment, where you can actually study those strategies because we've seen over and over again that it's hard to do that.

DR. PARSA: My name is Afshin Parsa. I voted no, and part of it is for reasons already stated. There are a lot of unknowns, but I think there might be room for areas where it can be used, and that goes back to areas where there are populations with high risk. Now, defining that, actually, unlike some other people, as a nephrologist, the 45 to 60, to me, is actually very much a high-risk population, and indeed other SGLT2 inhibitors are already approved in that category, and I see no reason why it would be different for this drug.

Regarding the 60 to 90 and the UACR of 30 to 30, there still probably is a broader number of people than I'm fully comfortable with, so higher proteinuria could be 200 or 300 but, again, that gets to an area in which one can already use them with that on empa. However, based on the comments by the type 1 diabetes societies, and the

patients, and the need for therapeutic options, which I very might appreciate, some things apply to everyone, like lipid lowering in someone with CVD or SGLT2 in type 2 diabetics with CKD, and other ones where for some people it works a lot better than the study population and these options.

I was thinking about who that might be, so for me, that would be 60 to 90 in terms of eGFR; a UACR greater than 30 with challenges to get glycemic control, and by that, two components. One is a high A1C despite real efforts by the patient and compliance that could be defined as 8.5, or 8, or whatever; or frequent hypoglycemic episodes because that is really a potential high benefit -- again, not to everyone, but for some patients they're just labile no matter what they do -- and then that would add an increased benefit that I think is compelling; and then, again, it goes back to the patient and their practitioner.

DR. SELIGER: Steve Seliger, and I voted no. I think we all heard, and I completely agree, that there is a great need for additional therapies for

people with this condition. I think my approach was to start with the determination of this committee back in 2019 for the whole indication, and I found substantial uncertainties in the data, both from an efficacy and safety standpoint, for the small subgroup that was being asked for. I don't have a particular recommendation for another GFR group. At least from the data that was available to us, I couldn't come up with one that would fit both rationally and with sufficient data.

DR. LOW WANG: Great. Let me summarize. The final vote was 3 yeses and 11 noes. I think the panel members talked about a clear unmet need for our patients with type 1 diabetes. Many panel members mentioned that probably the group with an eGFR category of 60 to less than 90 and UACR of 30 or higher might be a subgroup that could benefit from sotagliflozin, and possibly patients with difficulty getting to glycemic control, frequent hypoglycemia.

It was mentioned that there's enough information that we have right now to push this

discussion out to patients and their healthcare providers to let them decide, but then many people mentioned that there's a lot of uncertainty in the data. Several panel members didn't feel that the data supported a subgroup of patients with type 1 diabetes and CKD that would benefit, so we have lots of hypothetical reasons to believe that there's a benefit, but we have to be able to quantify them.

We don't necessarily need a trial that's as big as the cardiovascular outcomes trial. We could look at other outcomes, renal, et cetera, and patients with type 1 diabetes need to not be excluded from future trials. They need to be included in trials. So with that, we really don't know which subgroup would benefit the most, and we already have two other drugs in this class for heart failure and CKD with or without diabetes. We need adequate risk mitigation strategies. People mentioned ketone monitoring, continuous glucose monitoring. This wasn't really discussed in detail today, and there weren't data to support the

proposed strategies.

So overall, I think this was a really robust discussion, and I wanted to thank the panel members, the FDA, the applicant, the open public hearing speakers for the presentations and the discussion today. I also wanted to thank everyone who's listening. And before we adjourn, are there any last comments from the FDA?

DR. ARCHDEACON: I just want to thank everyone. This has been an incredibly helpful session for us, really thoughtful comments, and you've given us a lot to think about, so thank you again very, very much.

Adjournment

DR. LOW WANG: Thank you. We will now adjourn the meeting. Thank you.

(Whereupon, at 5:05 p.m., the meeting was adjourned.)