FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC)

Wednesday, November 13, 2019

8:00 a.m. to 4:15 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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C O N T E N T S

FDA Presentations

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. BURMAN: Good morning, and welcome. I would first like to remind everyone to please silence your cell phones, smartphones, and any other computer devices if you've not already done so. I would also like to identify the FDA press contact, Monique Richards. If you are present, please stand.

My name is Kenneth Burman. I'm the chairperson of the Endocrinologic and Metabolic Advisory Committee, and I will be chairing this meeting. The meeting is now called to order. We'll start by going around the table and introduce ourselves. We will start with the FDA to my left.

DR. YANOFF: Good morning. I'm Lisa Yanoff, acting director of the Division of Metabolism and Endocrinology Products in FDA.

DR. RAUSCHECKER: Good morning. I'm Mitra Rauschecker. I'm the acting clinical team leader

for the Division of Metabolism and Endocrinology Products for the FDA.

DR. NIYYATI: Good morning. I'm Dr. Mahtab Niyyati from the Division of Metabolism and Endocrinology Products, clinical reviewer from the FDA.

DR. PENZENSTADLER: Good morning. I'm Justin Penzenstadler. I'm the clinical pharmacology reviewer. I'm with the Office of Clinical Pharmacology in the FDA.

DR. BLAHA: Hi. Mike Blaha, professor of medicine and director of clinical research at Johns Hopkins Ciccarone Center for the Prevention of Heart Disease.

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

DR. DE LEMOS: James de Lemos. I'm a cardiologist at UT Southwestern.

DR. LOW WANG: Cecilia Low Wang, professor of medicine at University of Colorado and lead clinician scientist at CPC Clinical Research.

DR. PAI: Good morning. I'm Majunath Pai, associate professor of clinical pharmacy, University of Michigan.

LCDR BONNER: Good morning. I'm LaToya Bonner, DFO for EMDAC.

DR. BURMAN: Ken Burman, head of endocrinology at Medstar Washington Hospital Center and a professor at Georgetown University.

DR. MUNIR: Kashif Munir, endocrinologist, University of Maryland.

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

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

DR. WEBER: Good morning. Tom Weber. I'm an endocrinologist at Duke university in Durham, North Carolina.

MS. LELLOCK: Good morning. I'm Carling Lellock. I'm a patient representative.

DR. NASON: Good morning. Martha Mason. I'm a biostatistician at the National Institute of Allergy and Infectious Diseases, which is part of the NIH.

DR. KALYANI: Good morning. I'm Rita Kalyani, an adult endocrinologist in the Division of Endocrinology, Diabetes, and Metabolism at Johns Hopkins University School of Medicine.

DR. YANOVSKI: Hi. Jack Yanovski, pediatric endocrinologist at the National Institute of Child Health and Human Development, part of the National Institutes of Health.

DR. CHRISCHILLES: Good morning. My name is Betsy Chrischilles. I'm a pharmacoepidemiologist at the University of Iowa, Department of Epidemiology, College of Public Health.

DR. MEININGER: I guess, finally, I'm Gary Meininger. I'm an endocrinologist and head of pipeline development at Vertex Pharmaceuticals and serving as the industry rep for EMDAC.

DR. BURMAN: Thank you, all

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's 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 the conclusion. Also, the committee is

reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'll now pass the microphone to Commander LaToya Bonner, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

LCDR BONNER: Thank you.

The Food and Drug Administration is convening today's meeting of the Endocrinologic and Metabolic Drug 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 his or her 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 interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. 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 supplemental new drug application 204629/S-020 for empagliflozin oral tablet sponsored by Boehringer Ingelheim Pharmaceuticals, Incorporated for the following proposed indication: as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus. This is a particular matters meeting during which specific matters related to Boehringer Ingelheim Pharmaceuticals' sNDA a will be discussed.

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

product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Gary Meininger is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Meininger's role at this meeting is to represent industry in general and not any particular company. Dr. Meininger is employed by Vertex Pharmaceuticals.

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 the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. BURMAN: Thank you.

We will now proceed with the FDA's opening

remarks from Dr. Lisa Yanoff.

FDA Introductory Remarks – Lisa Yanoff

DR. YANOFF: Good morning. As I said, I am Dr. Lisa Yanoff, acting director of the Division of Metabolism and Endocrinology Products at the FDA, and I would like to welcome the advisory committee panel, the sponsors, and members of the public to today's meeting.

Diabetes mellitus is a serious chronic disease that affects over 30 million people in the United States. Approximately 5 to 10 percent have type 1 diabetes due to autoimmune beta cell destruction, usually leading to absolute insulin deficiency. For these patients, insulin is necessary therapy.

Patients with diabetes have an increased risk for micro- and macrovascular complications, and the main goal of therapy is to improve glycemic control to reduce the risk of complications such as diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy.

While it's established that patients with

diabetes are at increased risk for both microvascular and macrovascular complications, drugs for the treatment of diabetes are currently approved based on hemoglobin A1c, a glycemic-lowering surrogate.

HbA1c, or A1c, is formed by irreversible attachment of glucose to hemoglobin. It is directly proportional to the ambient glucose concentration, and it correlates with average blood glucose over the proceeding 2 or 3 months. A standardized assay is available, making this measurement reliable over time and across geographic regions.

For drug development, we consider A1c reduction to be a surrogate for benefit on microvascular disease. This is based on clinical trials that have established that glycemic lowering results in a reduction in the onset and progression of microvascular complications.

We now have 12 classes of drugs approved to improve glycemic control, however, only two classes, insulin and insulin analogs and the amylin

analog, pramlintide, are approved for use in patients with type 1 diabetes. FDA recognizes there is an unmet need for patients with type 1 diabetes to not only achieve better glycemic control for prevention of long-term complications, but also provide other tangible benefits that are important to patients, especially those that may affect day-to-day quality of life.

Certain drug classes that rely on an insulin independent mechanism of action have been explored for their potential use in type 1 diabetes. One of these classes is the SGLT2 inhibitor class. There are currently 4 SGLT2 inhibitors, which are FDA approved, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The first SGLT2 inhibitor approved was canagliflozin, followed by dapagliflozin, and empagliflozin, the topic of today's meeting, and more recently ertugliflozin. Two of these products also have additional indications for CV risk reduction in type 2 diabetes patients, but it's

important to note that these benefits have not been demonstrated in type 1 patients, and the mechanism of action of these benefits is not well understood.

Just to clarify, at this time, there are no SGLT2 inhibitors approved as adjunct to insulin in the treatment of patients with type 1 diabetes.

Empagliflozin, as with other SGLT2 inhibitors, acts at the SGLT2 receptor at the renal proximal tubule to inhibit reabsorption of filtered glucose in the kidneys, which results in an increase urinary glucose excretion, and thereby lowering plasma glucose levels.

The intended indication for empagliflozin is as an adjunct to insulin in adults with type 1 diabetes. While 10 milligram and 25 milligrams are approved for patients with type 2 diabetes, the applicant is proposing a lower currently unmarketed dose, 2.5 milligrams, for the type 1 diabetes population, for which the applicant believes has the most favorable benefit-risk profile among the doses that were studied.

Our agenda for the day is summarized here.

We will start with presentations from the sponsor before hearing presentations from the FDA. There will be time for questions after each of these sessions. We will then take a break for lunch, and after we return for lunch, we will have an open public hearing followed by the questions to the panel.

I'll now go through the questions for the day. Question 1, discussion question; discuss whether empagliflozin 2.5 milligrams, as an adjunct to insulin, provides benefit for adult patients with type 1 diabetes. Discuss your views of the clinical meaningfulness of the small HbA1c reduction, as well as other endpoints studied to evaluate benefits of empagliflozin 2.5 milligrams, including body weight and blood pressure.

Discuss your level of concern about the risk of diabetic ketoacidosis, or DKA, with the use of empagliflozin 2.5 milligrams in type 1 diabetes patients. Discuss your level of confidence and the ability of the available safety database to accurately characterize the DKA risk, given the

small number of events observed in a single trial that is only 26 weeks in duration.

Discuss your level of confidence in the reliability of the adjudication process to assess DKA risk, including the clinical meaningfulness of the adjudication categories and the applicability of extrapolating risk management in a clinical trial setting to real-world use.

Question 3 is also for discussion. Discuss the overall benefit-risk profile of empagliflozin 2.5 milligrams as an adjunct to insulin therapy for the treatment of adult patients with type 1 diabetes. Discuss the sufficiency of the demonstrated benefits in light of the uncertainties around DKA risk and other risks of the drug.

Question 4 is our voting question. Do the available data suggest that the benefits outweigh the risks and support approval of empagliflozin 2.5 milligrams administered orally, once daily, as an adjunct to insulin to improve glycemic control in adult patients with type 1 diabetes mellitus?

If yes, please explain your rationale and

comment on whether any additional studies should be required after approval. If no, please describe what further data you believe the applicant should provide to establish a favorable benefit-risk profile to support approval.

Thank you again for your participation today, and we look forward to an informative discussion.

DR. BURMAN: Thank you.

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

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

outcome of the meeting.

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

We will now proceed with Boehringer Ingelheim's presentation. Thank you.

Applicant Presentation - Jyothis George

DR. GEORGE: Good morning. Chairman, members of the advisory committee, FDA representatives, patients, and members of the public, my name is Jyothis George. I am an endocrinologist, and I have had the privilege to provide care for many patients with type 1 diabetes for more than a decade. Thank you for this opportunity to present and discuss our data.

Patients with type 1 diabetes live with multiple challenges: inconsistent glycemic control, weight gain, and the risk of hypoglycemia. The

unmet need in this population is to improve glycemic control without weight gain and without increasing the risk of hypoglycemia.

Type 1 diabetes is distinct from other types. Patients with type 1 are depending on insulin for their survival. The aim of new therapies is to work with insulin to improve glycemic control. Our proposal is for an adjunct therapy with a dose that is specific to type 1 diabetes. We are building this proposal on the foundation of our knowledge of SGLT2 inhibitors.

As you heard from Dr. Yanoff already, 4 SGLT2 inhibitors are approved in the United States for the treatment of type 2 diabetes. This includes empagliflozin, which is approved in over 100 countries with more than 7 million patient-years of cumulative exposure.

The glucometabolic mechanism of action is well known. The kidney is the primary site of action. These drugs increase glucose excretion in the urine, along with sodium, and along with water. This glucose excretion leads to the reduction in

HbA1c, C the long-term marker of glycemic control.

These reductions are dependent on blood glucose levels, therefore, the risk of hypoglycemia is inherently low. SGLT2 inhibitors also reduce body weight and blood pressure, clinical parameters that are important for public health given the high risk of cardiovascular and renal disease in these patients. Many sponsors have therefore attempted to repurpose this class of medicines as potential treatment for type 1.

As I discussed, one key benefit of SGLT2 inhibitors in this population is the improvement of glycemic control. This results in a reduction in insulin dosage. However, as patients with type 1 diabetes know, under insulin [indiscernible] can lead to an increased risk of DKA.

SGLT2 inhibitors can also induce ketogenesis, and together these factors can predispose patients to DKA, a well-known risk in all patients with type 1 diabetes. In other words, here is an inverse relationship between efficacy and safety. As efficacy improves, safety worsens.

Benefits and risks of SGLT2 inhibitors in type 1 were summarized in a recent meta-analysis. Expectedly, there is a reduction in HBA1c of 0.3 to 0.4, and body weight is also reduced meaningfully. However, there is also an increased risk of DKA.

Here is the data from sotagliflozin trials reviewed by this panel earlier this year. Both doses studied were associated with an increased risk of DKA. The data from dapagliflozin and empagliflozin showed an increased in the DKA rate in type 1 diabetes when using doses currently approved for type 2. In contrast, empagliflozin 2.5 milligram provided meaningful efficacy with a lower risk than the higher doses.

I will now summarize the key data for this proposed type 1 diabetes specific dose. This type 1 specific dose showed an improvement in HbA1c, but despite this HbA1c reduction, hypoglycemia was not increased. While weight typically goes up in HbA1c improvement, weight loss actually is observed here. Insulin reductions were lower in the proposed type 1 specific dose. More important, we did not

observe an increase in the DKA rate. In summary, the lower dose offered a favorable benefit-risk profile.

The need to balance safety and efficacy is a familiar concept for all of us involved in the care of patients with type 1. Too much insulin, and our patients develop hypoglycemia, illustrated here in red. Too little insulin, and there is suboptimal efficacy as shown in gray. The therapeutic sweet spot lies in the middle range shown in green.

The picture looks similar for SGLT2 inhibitors. High doses of these drugs could precipitate DKA, shown in red, requiring a type 1 diabetes specific dose that balances efficacy and safety, shown in the green area. However, developing a type 1 specific dose was not our initial intent. In fact, based on our experience with empagliflozin type 2 with 10- and 25-milligram doses, we were planning to register the same doses in type 1 as well.

In each one, we studied 2.5, 10, and 25 milligram, fully expecting that 10 and 25 milligram

would be the proposed doses. The efficacy and safety results of 10 and 25 observed in each one gave us the confidence in these doses. However, in the months that followed, FDA issued a warning on SGLT2 inhibitors and the risk of DKA. Therefore, during our phase 3 planning, FDA mentioned to us that safety concerns specific to patients with type 1 diabetes may warrant exploration of the lower dose.

The agency also questioned whether doses approved for type 2 diabetes are optimal for type 1 diabetes. Following this discussion, we added the 2.5-milligram dose of empagliflozin to one of our phase 3 trials, still expecting 10 and 25 milligram to be the appropriate doses for registration.

As our phase 3 trials read out, we saw there was an increased rate of DKA with 10- and 25-milligram doses in these type 1 diabetes trials. In 25 milligram, we saw a meaningful efficacy in HbA1c and other outcomes with no strong evidence of DKA. Therefore, we revisited our phase 2 studies. The efficacy seen with 2.5 milligram was consistent

across these three randomized-controlled trials. To provide supportive data, we conducted an exposure-response analysis.

There are many strengths to our program. The phase 3 randomized-controlled EASE-3, where 2.5-milligram dose was studied, meets many of the criteria for substantial evidence from a single trial. 189 sites were involved, and we employed 100 percent source data verification. There was high patient retention rate and low missing data. Multiple endpoints known to provide meaningful benefit to patients were positively impacted across multiple predefined subgroups. The primary endpoint, HbA1c reduction, had a highly persuasive p-value of 0.00003.

The pharmacology of empagliflozin is well characterized in type 2 diabetes and can inform decision making in type 1, too. Urine glucose excretion observed with the 2.5-milligram dose in type 1 diabetes is similar to the level observed in type 2 diabetes with empagliflozin 10 milligram.

In addition, there is supportive evidence

from two other randomized-controlled trials I mentioned earlier, EASE-1 and J-EASE-1, and there is also exposure-response analysis conducted in line with the best current practice, as well as regulatory guidance supporting the efficacy of empagliflozin 2.5 milligram. The totality of this evidence package provides us the confidence to seek an indication, an indication for empagliflozin 2.5 milligram as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes.

For this type 1 specific dose, we proposed to create and commercialize a dedicated brand of empagliflozin. This brand will have a name that is different from Jardiance, the currently approved type 2 diabetes brand name. We have obtained conditional approval from the FDA for a proposed new brand name.

Having this distinction in brands will help ensure that patients, physicians, and pharmacists can identify the right product, for the right patient, at the right time. Having a dedicated

type 1 diabetes brand will allow us to provide specific prescribing information so that prescribers and patients understand that the benefit-risk ratio of this lower dose applies only to patients with type 1 diabetes.

At the core of safe and effective use of any medicine is patient and professional education. Patients with type 1 are taught to recognize and initiate self-management of DKA. That recognition is integral to their every day survival. Most cases of DKA occur with blood glucose values more than 250 milligrams per deciliter, but it can also occur with blood glucose levels less than 250. This is likely to occur more commonly on patients treated with SGLT2 inhibitors.

We will highlight this atypical presentation to patients to minimize the delay in the diagnosis and treatment. We will reinforce education on avoiding those factors and the need to maintain adequate insulin dosing. Current American Diabetes Association standards of care recommend that ketosis-prone patients, like patients with type 1,

require ketone monitoring. We will reinforce this in all patient education material.

For physicians, education will focus on appropriate patient selection. These are patients with stable incidence regimes, are willing to accept the benefit-risk profile, and are able to avoid scenarios that places them at increased risk; for example, a very low carbohydrate diet. This importance of avoiding those factors and the need for cautious dose adjustment will be emphasized.

Diabetic ketoacidosis is a relatively rare event, which is inherently prevalent in this population. This is why we believe continuing surveillance in the postmarketing setting is important, and we are planning to do this. Our commitment to create a type 1 specific brand makes the postmarketing data collection specific to type 1 diabetes more feasible.

Our presentations this morning will provide further depth on our proposal for a type 1 diabetes specific dose, as well as the evidence base establishing positive benefit-risk for

empagliflozin 2.5 milligram. Professor Jennifer Green will remind us today, on the 13th of November, on the eve of World Diabetes Day, that patients with type 1 in the United States are still not able to control their blood sugars well.

Dr. Marquard, clinical development lead for empagliflozin and type 1 diabetes, will then present efficacy data. Dr. Schorling, who heads global patient safety for empagliflozin, will present safety data, as well as discuss the package of measures we believe are important to ensure safe and effective use of this medicine. Professor Perkins, principal investigator for empagliflozin and type 1, will put all this data into clinical context. I will then return to give closing remarks.

Now, I would like to welcome Professor Green to the podium.

Applicant Presentation- Jennifer Green

DR. GREEN: Good morning. My name is Jennifer Green. I'm an endocrinologist and professor of medicine at Duke University Medical

Center and a trialist at the Duke Clinical Research Institute. I am here today as a consultant to the sponsor. I am being compensated for my time and travel expenses. I do not have equity in the company, and I will not personally benefit from the outcome of today's meeting.

In my clinical practice, I routinely care for patients living with type 1 diabetes, and in my presentation, I will discuss unmet needs in the care of individuals with this condition. As you have already heard, type 1 diabetes is an autoimmune condition, which causes destruction of the insulin-producing beta cells of the pancreas. The hallmark of type 1 diabetes is hyperglycemia as a consequence of profound lifelong insulin deficiency.

Insulin treatment is essential in type 1 diabetes to reduce the risks of symptomatic hyperglycemia; life-threatening acute complications such as diabetic ketoacidosis, or DKA; and both microvascular complications, such as damage to the kidneys, eyes, and nervous system; and

cardiovascular complications.

Type 1 diabetes is estimated to reduce life expectancy by between 11 to 13 years, and with over 1 million Americans affected by the condition, it represents a major public health issue. There are very significant challenges in the treatment of type 1 diabetes, and management generally requires a complicated regimen of care. This usually includes intensive insulin therapy delivered through multiple daily injections and/or inhalations or use of an insulin pump, and frequent glucose testing via finger sticks or use of a glucose sensor.

There is one non-insulin therapeutic option, pramlintide, which is approved for use in the U.S. as an adjunct to insulin therapy, and I'll discuss that in greater detail later in my presentation.

Despite this complexity of delivered care, people with type 1 diabetes often struggle to find a balance between good overall blood sugar control and the risk of hypoglycemia due to their insulin therapy. Diabetic ketoacidosis, or DKA, is an

acute complication which is inherent to type 1 diabetes, and the majority of persons with type 1 diabetes have experienced at least one episode of DKA. Current annualized rates of DKA are 2 to 6 per 100 patient-years, but fortunately, the current U.S. case fatality rate is far lower, at about 0.4 percent of patients who have an episode of DKA.

DKA prevention is an integral part of type 1 diabetes management. Patients should be routinely educated on precipitating factors and detection of and management of ketosis should it occur. The American Diabetes Association, or ADA, has published recommendations for a sick-day management and use of ketone monitoring to detect signs of DKA early and ensure prompt management should it occur.

Glycemic control is the fundamental means of reducing the risk of complications in people with type 1 diabetes. In the landmark DCCT interventional trial and EDIC follow-up study, patients who were originally assigned to intensive glycemic control with achievement of a hemoglobin A1c near 7 percent did have significantly reduced

risks of retinopathy, nephropathy, and neuropathy at 6 and a half years, compared to patients who received more conventional glycemic control, which resulted in a hemoglobin A1c of around 9 percent.

The patients assigned to intensive glycemic control also had a 57 percent reduced risk of cardiovascular complications after a mean 17 years of follow-up, and this included both the initial interventional trial period and a subsequent observational follow-up period. These findings provide justification for current glycemic treatment targets, generally a hemoglobin A1c of below 7 percent, in the care of people with type 1 diabetes. In addition, hemoglobin A1c lowering is an accepted surrogate for reducing the risk of complications in type 1 diabetes.

Hemoglobin A1c lowering translates into meaningful reductions in the risk of complications in type 1 diabetes. This slide shows data from a DCCT and EDIC based type 1 diabetes model used to stimulate the incidence microvascular complications in patients experiencing A1c reductions between 0.1

and 0.8 percent from a baseline of 7.9 percent.

In this model, a modest hemoglobin A1c reduction, for example of about 0.25 percent, translates into a projected approximately 8 percent reduction in the risk of retinopathy and in approximately 5 percent reduction in the risk of microalbuminuria over time.

However, despite the known benefits of good glycemic control, many people with type 1 diabetes are not well controlled, and data from the type 1 diabetes exchange clinical registry, which includes over 30,000 individuals with type 1 diabetes across the U.S., has shown that the mean achieved A1c in that group between 2016 and 2018 was 8.4 percent, so this was significantly above the recommended goal of less than 7 percent.

Unfortunately, this appears to have changed little over the proceeding decade despite continuous advances in insulin formulations, insulin delivery devices, improvement and approaches to diabetes education, and team-based care over that time. Very common barriers to

achievement of glycemic control in type 1 diabetes include the risks of hypoglycemia and weight gain associated with insulin therapy, as well as problems related to regimen complexity.

Hypoglycemia very often accompanies intensive management of type 1 diabetes, and this slide shows that in the previously mentioned Diabetes Control and Complications Trial, or DCCT, tighter glycemic control with insulin therapy was associated with a corresponding and continuous increase in the risk of severe hypoglycemia.

Also from the DCCT, we've learned that people with type 1 diabetes treated more intensively with insulin and gained more weight over time than did people assigned to more conventional blood sugar management.

This slide shows the proportion of patients with major weight gain; that is a more than 5 kilogram per meter squared increase in body mass index, or BMI, occurring during that trial. And as you can see, the intensively treated men and women were more likely to experience this degree of

increase in BMI, and the risk appears to have steadily increased over time.

So what are the patient priorities in the management of type 1 diabetes? As an example, this slide shows the results of a survey of more than 1,000 affected people and more than 300 spouses of individuals with type 1 diabetes. The graphics show the ranking of patient priorities in diabetes care at the top by unmet needs scores.

Some of the issues prioritized by patients in this survey included a need for simple and predictable diabetes management, hemoglobin A1c improvement and control, prevention of weight gain, and prevention of hypoglycemic events. The issues most likely to cause emotional distress in the spouse are shown at the bottom, and you can see that the issue most likely to cause distress for the spouse was worry about partner hypoglycemia.

Of note, more than half of partners reported that they'd personally help their partner with type 1 diabetes to recover from at least one severe hypoglycemic episode within the past 6 months.

So what is the unmet need in type 1 diabetes management? We need more options to improve glycemic control without weight gain and without increasing the risk of hypoglycemia.

There are limited choices for use of medicines as adjuncts to insulin therapy. Pramlintide, as previously mentioned, is the only therapy approved in the U.S. to use as an adjunct insulin therapy in type 1 diabetes management, and the drug provides hemoglobin A1c reductions of approximately 0.3 percent and weight reduction of about a kilo. However, its use is limited by its dosing complexity and side effect profile.

As you can see, despite availability of the drug since 2004, it is not widely used. In a recent type 1 diabetes registry report, only 1.6 of those included were using pramlintide as part of their diabetes care regimen. In fact, more patients are using unapproved adjunct therapies such as Metformin, GLP-1 receptor agonist, or SGLT2 inhibitors for the management of type 1 diabetes than are using the approved medication option.

As Dr. Robert Ratner has previously asked, "How do we make life better, not just longer, for people with diabetes?" We need more options to improve glycemic control without weight gain and without increasing the risk of hypoglycemia. An option which also reduces cardiovascular risk factors such as blood pressure and weight would be an added advantage. These options should be convenient for patients to use and should be regulated by the FDA.

Now, Dr. Marquard will review the EASE phase 3 program and efficacy results.

Applicant Presentation - Jan Marquard

DR. MARQUARD: Good morning. My name is Jan Marquard. I am a pediatrician by training and lead of the empagliflozin and type 1 diabetes clinical development program at Boehringer Ingelheim. The efficacy data package for empagliflozin 2.5 milligram is drawn from three sources: phase 3 trials, phase 2 trials, and exposure-response simulation studies.

As you heard, we originally designed the

phase 3 program to seek registration for empagliflozin 10 and 25 milligram, but after reviewing the phase 3 data, we pivoted toward the 2.5 milligram dose because it offered an acceptable balance of benefit and risk in patients with type 1 diabetes.

Although we are not seeking an indication for the higher doses, we will present the empagliflozin 10- and 25-milligram data to provide context for interpreting the results from 2.5. These data from the higher doses also demonstrate the risk relationship between high efficacy and increased risk.

The phase 2 studies, EASE-1 one performed in Europe and J-EASE-1 performed in Japan, provide additional clinical data supporting the efficacy of empagliflozin in patients with type 1 diabetes. Since empagliflozin 2.5 milligram was included in only one of the phase 3 trials, we decided to conduct exposure-response simulation studies to see if the effect of the low dose would be confirmed in the EASE-2 setting.

We simulated the effect of a 2.5-milligram dose in the EASE-2 clinical trial that did not test this dose. EASE phase 3 consisted of two randomized, double-blind, placebo-controlled trials. These trials were conducted across 310 sites, mainly in North America and Europe, ensuring the EASE global data are applicable to the U.S. population and relevant for U.S. medical practice.

Our main objective was to evaluate the safety and efficacy of empagliflozin 10- and 25-milligram doses, plus a lower dose of 2.5 as adjunct to intensified insulin in patients with type 1 diabetes. The population studied was generally young and healthy with a need to improve glycemic control.

The program was not designed to assess micro- or macrovascular outcomes such as progression of kidney disease or myocardial infarction. Trial design and conduct were slightly different: inclusion of empagliflozin 2.5 milligram, a shorter treatment duration, and the assessment of continuous glucose monitoring as a

substudy in EASE-3 only.

An important part of the design of both trials was the therapy intensification period. This period was established because we wanted to evaluate the effect of empagliflozin in those patients who had a need to further improve glycemic control despite their best efforts to do so with diet, exercise, and insulin alone.

Following randomization, investigators were advised to adjust the patient's total daily insulin dose based on needs. For patients with A1c below 8 percent at baseline, there was a recommendation to reduce the insulin dose by 10 percent to avoid hypoglycemia.

Thereafter, adjustment to insulin therapy could be implemented throughout the studies based on investigator judgment. This enabled an individualized but harmonized approach to achieve best placebo control. Since the impact of flozin 2.5 milligram dose was not evaluated in the long-term try EASE-2, the effect was evaluated in an exposure-response simulation study.

The primary endpoint in both studies was the change from baseline in A1c at week 26. According to FDA's guidance for purposes of drug approval and labeling, demonstration of efficacy should be based on reduction in A1c. This guidance is based on the evidence from the DCCT and EDIC studies that have demonstrated clinical benefits in patients who achieve better glucose control in terms of delaying the chronic complications of type 1 diabetes.

Additional endpoints beyond A1c are highly relevant for patients with type 1 diabetes. Therefore, we selected key secondary endpoints such as investigator reported symptomatic hypoglycemic events, including severe hypoglycemia; change from baseline in body weight and total daily insulin dose; and systolic and diastolic blood pressure. Continuous glucose monitoring parameters, including time and range, were assessed as key secondary endpoint in EASE-2 only. However, these parameters were also evaluated in EASE-3 based on data from a substudy.

The primary efficacy analysis included

on-treatment data only on the full analysis set, including all treated patients with a baseline and with equal or more than one on-treatment A1c measurement. Subsequently, an effectiveness analysis, including data after treatment discontinuation, was performed hierarchically on the modified intention-to-treat set, including all treated patients with a baseline and with equal or more than one post-randomization A1c measurement.

In the first step, we tested A1c efficacy and effectiveness for 10 and 25 milligram. If null hypotheses were rejected, then sequentially the primary efficacy endpoint for empagliflozin 2.5 milligram in EASE-3 and key secondary en points in both trials were to be tested for empagliflozin 10 and 25 milligram versus placebo in the hierarchical order shown on this slide.

To clarify, the only confirmatory analysis for the 2.5-milligram dose is the A1c reduction based on the full analysis set after 26 weeks, reflecting the initial intent of the clinical development program to register only the higher

doses. Key secondary endpoints were included in the confirmatory testing hierarchy for empagliflozin 10 and 25 milligram only.

We selected the analysis based on the full analysis set as primary analysis because physicians and their patients are primarily interested in the expected individual therapeutic effect for an adherent patient. The effectiveness estimates by contrast combines information from adherent and nonadherent patients into one estimate for the entire population. I will present the data from both analysis sets.

Adult patients aged 18 years and older with a diagnosis of type 1 diabetes for at least one year were eligible for inclusion in the trials. Based on the investigator's judgment, patients must have had a good understanding of their disease and how to manage it, and be willing and capable to comply with study requirements. These requirements included insulin adjustment, blood glucose and ketone monitoring, recognizing symptoms of DKA, and implementing a sick day management plan.

Patients had to be on multiple daily insulin injections or insulin pump therapy. The A1c range of 7.5 to 10 percent at randomization enabled the inclusion of a broad population of patients with type 1 diabetes at less than optimal glycemic targets despite insulin intensification.

The body mass index had to be equal or more than 18.5, and the estimated glomerular filtration rate had to be equal or more than 30. Patients with a history of diabetic ketoacidosis and/or severe hypoglycemia were included unless there was an episode in 3 months prior to screening and after randomization. Patients with eating disorders were excluded.

Baseline characteristics were well balanced between the treatment arms within each study. Approximately half of the patients were female, most patients were recruited in North America and Europe, and 95 percent were Caucasian. The mean age was 43 to 45 years. Blood pressure was well controlled. The mean body mass index was in the overweight range. Most patients had good kidney

function.

The majority had been living with diabetes for over 20 years. A1c at baseline, following the insulin intensification period, was 8.1 to 8.2 percent. The insulin dose at randomization was 0.7 units per kilogram, and around 60 percent were using multiple daily insulin injections and 40 percent using insulin pumps.

Baseline characteristics were generally balanced between U.S. patients and patients elsewhere. More pump use was noted in the U.S. population where there's non-U.S. patients with 60 percent pump use in the U.S. population versus 30 percent in the non-U.S. population. The baseline characteristics of U.S. patients were comparable with data reported from the type 1 exchange registry and data from contemporary observational studies in the United States.

Overall, 977 patients were assigned to treatment in EASE-3, while 730 were assigned to treatment in EASE-2. Overall, approximately 90 percent of patients completed treatment at week 26.

In the 2.5-milligram group, 93 percent of patients completed treatment and 96 percent completed the trial. Before reviewing the results for the primary endpoint at week 26 in EASE-3, I will present the A1c change during the lead-in period prior to randomization.

As previously mentioned, it was an important aspect of the phase 3 trials to study the effect of empagliflozin as adjunct to intensified insulin therapy. During the therapy intensification period, investigators were advised to optimize each participant therapy based on local guidelines. This was effective and resulted in an A1c reduction of approximately 0.5 percent. Then patients were randomized, and over time, A1c increased in patients on placebo.

This increase reflects the clinical challenge for patients to adhere to recommendations to healthy diet, exercise, frequent glucose monitoring, and thorough insulin adjustment over an extended period. But with empagliflozin, there was a dose-dependent improvement in A1c over time with

an expected increase in A1c after 4 to 12 weeks.

At 26 weeks, patients on empagliflozin had significantly better A1c values than patients on insulin alone. The change from baseline, based on the full analysis set, was minus 0.28 percent with empagliflozin 2.5 milligram. Results were almost identical based on both the modified intention-to-treat analysis and further sensitivity analysis.

The results for the efficacy and effectiveness analysis were clinically meaningful and highly statistically significant with p-values less than 0.0001. Based on the primary efficacy analysis, the A1c reduction with empagliflozin 10 and 25 milligram was minus 0.45 and minus 0.52 percent, respectively. These results were consistent based on the effectiveness analysis.

The A1c reduction with empagliflozin 2.5 milligram was generally consistent across all prespecified subgroups. No relevant changes were observed for U.S. versus non-U.S. patients, sex, age, and body mass index. For the subgroups, based

on time elapsed since diagnosis, a treatment by subgroup interaction at the 10 percent level it was observed.

For empagliflozin 2.5 milligram, the change from baseline in A1c with placebo was minus 0.81 in patients with no more than 5 years since diagnosis. However, this result is based on a very low number of patients, and no clear differences were observed for the 10- and 25-milligram doses for this subgroup parameter.

Overall, the data support the conclusion that time since diagnosis has no relevant impact on A1c reduction on the empagliflozin treatment in patients with type 1 diabetes. For patients with eGFR below 60, no benefit in terms of A1c reduction was observed. Similar results were observed for empagliflozin 10- and 25-milligram doses for this subgroup. Despite a non-significant treatment by subgroup interaction and the low number of patients, empagliflozin 2.5 milligram would not be recommended in this population with eGFR below 60.

Recent data from the type 1 exchange

registry show a mean A1c above 8 percent across a large segment of the population. Therefore, it is important to look more closely into this subgroup consisting of 60 percent of the EASE-3 population. The placebo-corrected A1c reduction with empagliflozin 2.5 milligram in patients with baseline A1c between 8 to 9 percent, with minus 0.33 percent and minus 0.51 percent in patients with baseline A1c greater or equal to 9 percent, these data suggest greater efficacy of empagliflozin 2.5 milligram in patients with higher baseline A1c.

With regard to body weight, there was a significant reduction with all empagliflozin doses. The 2.5-milligram dose resulted in a mean reduction of 1.8 kilogram at week 26. Body weight was stable on placebo while it decreased on empagliflozin. In EASE-3, a clear dose dependency in insulin dose reduction was observed with the reduction of 6 percent with empagliflozin 2.5 milligram and up to 13 percent with empagliflozin 25 milligram.

The reductions in basal and bolus insulin

doses were evenly distributed. The need to reduce the insulin dose when initiating empagliflozin occurred shortly after the start of treatment. The total daily insulin dose was largely stabilized by week 4. The insulin incidence dose reduction itself is a known risk factor for DKA, so these results are also relevant from a safety perspective.

We also saw reductions in systolic blood pressure. All empagliflozin doses reduced systolic pressure by 2 to 4 millimeters of mercury. The observed empagliflozin mitigated reductions in blood pressure potentially have beneficial effects on macrovascular outcomes in patients with type 1 diabetes.

Time in glucose target range assessed by continuous glucose monitoring is an important outcome in patients with type 1 diabetes. These pie charts show the three categories of time and range and time spent in hyper- and hypoglycemia over 24 hours for each treatment group at baseline.

Time and range, defined as time spent with

blood glucose between 70 to 180 milligrams per deciliter is shown in green. Time spent over 180 milligrams per deciliter is presented in yellow, and in red, time spent below 70 milligrams per deciliter. At baseline, all treatment groups were comparable.

The CGM substudy showed a trend for empagliflozin 2.5 milligram to increase the time spent in the target range by 1 hour per day. This effect was mainly driven by reduction of time spent in hyperglycemia. The EASE-2 results for the primary and key secondary endpoints for empagliflozin 10 and 25 milligram were consistent with the results from EASE-3. The placebo-corrected A1c reduction with empagliflozin 10 and 25 milligram was approximately 0.5 percent after 26 weeks.

Reductions in body weight were around 3 kilogram. The time spent in target glucose range was increased by approximately 13 percent, which translates in 3 additional hours per day in glucose target range. Patients reduced the total insulin

dose by 13 percent. In addition, reductions in systolic and diastolic blood pressure were observed in the range of 2 to 3 millimeters of mercury. The detailed results are reported in the briefing document. Of note, all effects were sustained over 52 weeks.

We also evaluated hypoglycemia across both trials and all doses. In general, data from the higher doses will have to establish the upper bound for potential risks of the 2.5-milligram dose. From this perspective, the data for empagliflozin 10 and 25 milligram are important to understand the impact of empagliflozin on hypoglycemia in patients with type 1 diabetes. Before reviewing the results from the EASE clinical program, I will provide some background regarding the hypoglycemia definitions used.

The key secondary hypoglycemia endpoint was a composite endpoint, including investigator reported symptomatic hypoglycemic adverse events with blood glucose below 54 milligrams per deciliter and/or severe hypoglycemic events. As

depicted on the slide, these events are a subset of all hypoglycemic events with blood glucose below 54 milligrams per deciliter and subjective judgment may influence their reporting.

Severe hypoglycemia with severe cognitive impairment, requiring external assistance for recovery, was part of the key secondary hypoglycemia endpoint. Since this is the most severe presentation of hypoglycemia and life-threatening complications in patients with type 1 diabetes, I will review these results separately.

During the conduct of phase 3, the joint position statement on hypoglycemia reporting in clinical trials of the American Diabetes Association and the European Association for the study of diabetes was published. Based on this, we prespecified a third hypoglycemia analysis. In addition to the key secondary hypoglycemia analysis, based investigator reporting, we also assessed all patient reported hypoglycemia events with blood glucose below 54 milligrams per

deciliter, irrespective of symptoms.

For empagliflozin 2.5 milligram, no significant treatment difference was observed based on the key secondary hypoglycemia analysis. Hypoglycemic episodes requiring assistance were adjudicated by an independent clinical event committee. Empagliflozin 2.5 milligram did not increase the risk of severe hypoglycemia.

The broadest hypoglycemia analysis, based on all patient-reported events with blood glucose below 54 milligrams per deciliter, showed a trend towards a reduction of these serious and clinically important events. The hypoglycemia results for the higher doses were generally consistent with the findings for empagliflozin 2.5 milligrams with significant reductions in patient-reported events with blood glucose below 54 milligrams per deciliter.

Based on the totality of hypoglycemia results, we conclude that empagliflozin did not increase the risk of hypoglycemia in patients with type 1 diabetes.

To measure patient treatment satisfaction with empagliflozin, we used these established Diabetes Treatment Satisfaction Questionnaire, DTSQ. In a patient-centered healthcare system, it is increasingly important to enable the patient's voice to be heard when assessing the value of new healthcare options. In EASE-3, the DTSQ total score was significantly increased with empagliflozin treatment after 26 weeks. This effect was similar in EASE-2 and sustained over 52 weeks. These data are shown in the briefing document.

To contextualize these data, we provide the results from studies evaluating new insulin analogs that have replaced human insulin and intermediate acting insulin; hence, a standard of care. The improvement in the treatment satisfaction with empagliflozin 2.5 milligram was similar in magnitude to higher doses of empagliflozin. It was also similar to what has been observed historically with the short-acting insulin analog aspart and the long-acting insulin analog glargine to highly

effective treatments for patients with type 1 diabetes.

I will now review the supporting data from the randomized-controlled phase 2 study EASE-1. The results from the Japanese phase 2 study J-EASE-1 were, overall, consistent with the findings from EASE-1 and are reported in the briefing document. Despite small sample sizes and short treatment duration, the results of the phase 2 studies were also consistent with the results from phase 3.

In EASE-1, empagliflozin 2.5, 10, and 25 milligram were tested over 4 weeks. All patients were Caucasian Europeans with more males, a mean age of 41, a BMI of 26, and a mean A1c at baseline of 8.2 percent. The primary endpoint in EASE-1 was the assessment of urinary glucose excretion, the main pharmacodynamic parameter of SGLT2 inhibitors.

Empagliflozin 2.5 milligram provides 70 percent of the effect of the higher doses, providing evidence of a meaningful pharmacodynamic effect of the lower dose that translates into meaningful efficacy results. In EASE-1, all doses

of empagliflozin studied were comparable in efficacy and improved glycemic control with weight loss with increased time in glucose target range and without increasing hypoglycemic events. The placebo-corrected A1c reduction with empagliflozin 2.5 milligram was minus 0.35 percent. No DKA events were reported.

I will now present the results from the exposure-response simulation studies. In order to understand the data of the exposure-response simulation studies, it is important to understand the general concept of an exposure-response simulation trial.

This study combines an exposure model component that describes the concentration time course of a drug in the blood and the response model component, in our case A1c, that relates the blood concentration to the drug effect. Taken together, this describes the time course of the effect for a specific dose.

As a first step, we had to build the exposure-response model. For model development, it

was important to not use the data from EASE-3 because we wanted to confirm the empagliflozin 2.5-milligram effect independently of these results. This is why we used data from the phase 2 study EASE-1 and the phase 3 study EASE-2. In addition, we used previous knowledge from exposure-response analysis conducted in patients across all available patient populations.

The developed model was able to describe the time course of A1c lowering in all dose groups in the EASE-2 populations up to 52 weeks of treatment. The dots represent the observed data from EASE-2, and the lines, the simulated profiles with 95 percent confidence intervals.

Second, the model was validated using EASE-3 data. We were able to replicate the results for all dose groups observed in E-3 by clinical trial simulations. Simulating the outcome of a study that is not included in the exposure-response analysis is considered the gold standard for model validation. The model validation supports the conclusion that the model was suitable to conduct

clinical trial simulations to investigate untested scenarios.

At the third and last step, we conducted the clinical trial simulations to evaluate the effect of the 2.5-milligram dose in the EASE-2 population. For this purpose, 500 trials were simulated with the same number of patients included in the EASE-2 study per dose group. The simulated, placebo-corrected A1c reduction in EASE-2 with empagliflozin 2.5 milligram was minus 0.29 percent after 26 weeks.

These consistent results confirmed the A1c reduction of empagliflozin 2.5 milligram in EASE-3. Of note, the data suggest that the simulated effect was sustained over 52 weeks. These results are important because they provide additional evidence of empagliflozin 2.5 milligram efficacy independent of EASE-3.

To summarize, we observed clinically meaningful A1c reductions with empagliflozin 2.5 milligram across phase 3, phase 2, and exposure-response simulation studies in the range

of 0.3 percent. The A1c reduction was modest but meaningful since any decrease in A1c without substantial hypoglycemia or weight gain is desirable in patients with type 1 diabetes.

The consistent effect on A1c reduction is complemented by improvements of important glucometabolic findings, including reductions of body weight and blood pressure, together with increased treatment satisfaction. No increased risk of hypoglycemia was observed.

Dr. Schorling will now discuss the safety results.

Applicant Presentation - Ona Kinduryte Schorling

DR. SCHORLING: Good morning. My name is Ina Kinduryte Schorling. I am global head of the drug safety department for metabolism at Boehringer Ingelheim.

Dose-dependent efficacy improvements with SGLT2 inhibitors are linked to a dose-dependent increase in DKA. It is therefore important to evaluate safety results before selecting the dose with the most favorable benefit-risk profile.

Empagliflozin 2.5 milligrams safety data will be presented versus placebo on the trial level. Empagliflozin 10- and 25-milligram data helped to establish the upper bound for general safety of the 2.5-milligram dose. For this reason, data on 10- and 25-milligram doses will be presented pooled across the trials.

Total exposure for empagliflozin was 809 patient-years of which 117 patient-years was on empagliflozin 2.5 milligram. I will start with the general safety. Overall, adverse events occurred with similar frequency in empagliflozin 2.5 milligram and placebo arms. As expected, a numerical increase in drug-related adverse events by investigator and adverse events leading to discontinuation could be explained by known effects of SGLT2 inhibitors. These include genital urinary tract infections and ketosis-related events.

Serious adverse events were balanced between treatment arms. Overall, the same pattern was seen with the higher doses. One patient died in 25-milligram group during in-hospital treatment of

DKA. The details of this case are presented in the briefing document, and we are prepared to discuss if needed.

For the 2.5-milligram dose, the proportion of patients with investigator- reported DKA events was similar between the 2.5-milligram dose and placebo. With the 10- and 25-milligram doses, there was an increase in DKA as compared to placebo. Further adverse events of special interest were defined and analyzed based on previously identified safety data within the drug class.

As already shown in the efficacy presentation, severe hypoglycemia occurred with similar frequency between treatment arms. As expected, an increase in genital infections was observed. The relative increase compared to placebo was lower with the 2.5-milligram dose than with the higher doses. For the remaining events of special interest, no clinical and meaningful differences were seen between the treatment arms. As DKA is the primary event special interest for

assessing benefit-risk. The remaining part of my presentation will focus on DKA.

All investigator-reported adverse events indicated for DKA were sent for adjudication in a blinded fashion by an external independent adjudication committee. This committee adjudicated cases based on predefined case categories and clinical judgment. To ensure this committee was reviewing the broadest set of cases possible, elevated patient-measured ketones were also sent for adjudication irrespective of symptoms.

This data summarizes the medical concept employed in our case definitions. For the diagnosis of certain DKA, the committee used the American Diabetes Association definition. If both acidosis and ketosis were present, the event was adjudicated as sudden DKA. In addition, recognizing that all data may not be available to adjudicate all cases, the FDA recommended implementation of case definitions that spanned from certain to unlikely. Therefore, we broadened the adjudication process and added a category of

unlikely DKA and a category of potential DKA.

For example, if there was confirmed absence acidosis, the case was considered unlikely to be DKA. If symptoms of DKA were present with either acidosis or ketosis, the episode was to be adjudicated as potential DKA. In addition, if there was persistent high ketones, irrespective of symptoms or acidosis, these cases were also classified as potential DKA.

Events reviewed by the adjudication committee with non-persistent increased ketones and without evidence of acidosis or symptoms of DKA were classified as ketosis. For example, a patient who was described in the FDA briefing book had a high glucose and was found to have elevated ketones but no symptoms and normal pH with a value of 7.43 by blood gas analysis. Because of normal pH, this case was adjudicated as unlikely DKA but ketosis.

Looking at adjudicated events, there was no imbalance in the frequency and event rate of sudden DKA for empagliflozin 2.5 milligram. The two episodes reported in the 2.5-milligram arm were

assessed by the adjudication committee as mild, based on the level of acidosis and the degree of symptoms.

For completeness, we included episodes adjudicated as potential DKA. Four patients in each group had sudden or potential DKAs. None of the potential DKA episodes in the 2.5-milligram dose led to hospitalization. More patients with a 2.5-milligram dose had unlikely DKA but ketosis. In the analysis of investigator-reported DKAs and adjudicated DKAs shown here, irrespective of whether we looked at sudden DKA on its own or sudden and potential DKA together, no imbalance in the event rate was observed. This is consistent with what has been seen for investigator-reported events.

This figure summarizes totality of investigator-reported DKAs and adjudicated DKAs across all doses. At all doses, concordance was seen between investigator-reported events and adjudication results. To fully explore the risk of DKA over time, we considered both sudden and

potential DKA events.

This figure shows time to first episode of either sudden or potential DKA in EASE-3 and EASE-2. The shaded area represents the same time period up to 26 weeks, which makes comparison easier. The proportion of patients with at least one episode of sudden or potential DKA during this period was similar with 10- and 25-milligram doses. DKAs were distributed equally over time in both trials for these two higher doses.

The rate of sudden or potential DKA, except with 2.5 milligram, was lower than that of 10 and 25 milligram. In addition, there was no time dependency for sudden or potential DKA the 2.5-milligram dose EASE-3. Taken together, this suggests that the observed pattern of sudden and potential DKA risk for 2.5 can be expected to follow a similar pattern for up to a year.

In addition to sudden and potential events, it is of clinical interest to define additional cases, which could have progressed to DKA. The broadest analysis for this includes events

adjudicated as sudden DKA, as potential DKA, as unlikely DKA but ketosis, and all ketone values above 1.5 millimoles per liter, irrespective of whether they met adjudication through your criteria.

This analysis shows a rate ratio of 1.65 with confidence intervals crossing cumulative [indiscernible]. Let me put this in context of the other analysis for the risk of DKA with 2.5 milligram. As you have seen, the rates of investigator-reported and adjudicated DKA are similar and balanced between 2.5-milligram dose and placebo. Some risk factors for DKA are well known.

Also, in our studies, the patients who developed sudden DKA had at least one typical precipitating factor such as acute illness, inadequate insulin administration, including pump failure, or carbohydrate depletion. Therefore, even though we observed no imbalance with 2.5 milligrams, it is important to inform patients about these risk factors.

The lower incidence of DKA for empagliflozin

2.5 was observed in our clinical trials with risk mitigation measures in place for all doses. Here is a summary of mitigation measures in our clinical trials. Investigators were trained on the risk of DKA, including the atypical presentation and caution around insulin dose adjustment.

Patients received and used a point-of-care device to measure ketones and an electronic diary for daily recording of ketone measurements and symptoms suggestive of the DKA. Patients were instructed to measure ketones 2 to 3 times a week or in case of any symptoms, regardless of glucose levels. Patients were also advised to seek medical care in case of ketone levels above 1.5 millimoles per liter.

Additionally, during this study and after occurrence of the fatal DKA event, a trial information card was implemented. This card highlighted the need for measuring ketones in case of symptoms indicative of DKA, irrespective of blood glucose levels. We understand that the risk of DKA might be higher in a postmarketing setting.

Therefore, to enhance measures beyond what we had in clinical trials, we proposed the following measures to discuss with the FDA.

Our proposed measures are based on experience from clinical trials, as well as BI's [indiscernible] experience in communicating with patients and prescribers. We also consulted with patient representatives and prescribers, and our proposed measures are in line with the published recommendations from medical experts.

Healthcare providers will see a distinctive separate brand from the empagliflozin type 2 brand. This will allow us to focus on type 1 diabetes specific DKA risk mitigation measures such ketone monitoring and will also help to reduce the risk of potential medication errors. Healthcare providers will be instructed to prescribe this product only to patients who are on stable insulin regimen, who do not have eating disorders, can abstain from low carbohydrate diets and excessive alcohol intake, and are who willing to adhere to insulin adjustments, glucose, and ketone monitoring.

Further, we will provide guidance to prescribers on careful insulin dose adjustments and discontinuation in situations known to predispose patients to ketoacidosis such as acute illness, surgery, or insulin pump malfunction. Prescribers will be instructed to counsel patients about ketone monitoring, interpretation of ketone values, and associated actions such as following a sick-day protocol and ensuring adequate hydration. Education regarding atypical DKA will be targeted to patients, prescribers, and emergency care providers.

One of the most important pieces of information for patients are the potential life-threatening consequences of DKA. Patients will have detailed instruction in the medication guide on how to avoid known risk factors of DKA, when to measure ketones, which actions to take in case of elevated ketone levels, and when to seek medical care.

A wallet card will be dispensed to patients with each prescription, and they will be instructed

to carry the wallet card with the at all times. The card will provide an easily accessible quick reference that highlights the most important information from the medication guide regarding ketoacidosis for the patient and for emergency care providers.

Importantly, this information will be available in hard copy and on patient's smartphone in digital format to ensure easy accessibility in patients' daily life. We will make every effort to provide patients with continuous education, and we'll collaborate with patient advocacy groups and physicians to develop these resources.

To summarize, no new safety signals besides known effects of empagliflozin were identified in our phase 3 program. There was no imbalance in the frequency of DKA between 2.5 milligram and placebo, indicating that the low-dose selection itself is an important factor for DKA risk mitigation in patients with type 1 diabetes. However, we understand the limitations of the clinical development program, and that the DKA risk cannot

be excluded in the real-world cues.

That's why we have designated a specific brands with the 2.5-milligram dose for type 1 diabetes. As part of this specific type 1 diabetes brand distinction, we will work with the FDA on implementation of necessary measures to minimize the risk of DKA in the postmarketing setting.

Now, Professor Perkins will present the clinical implications and his own clinical perspective.

Applicant Presentation - Bruce Perkins

DR. PERKINS: Thank you, Dr. Schorling.

I'm Bruce Perkins. Today I serve as a consultant. I've been compensated for my time, and I don't stand to personally benefit from the ultimate FDA decision. I'm an endocrinologist, an epidemiologist, a clinician scientist, and the director of the Leadership Sinai Centre for Diabetes at the University of Toronto. My clinical practice and my research focuses on type 1 diabetes, and I served as a coordinating investigator in the phase 3 EASE program in type 1

diabetes.

I wanted to admit to you that my professional opinions are very much flavored by the fact that as a teenager, I was presented with a diagnosis of type 1 diabetes myself, and it's become my core mission to find ways to help people with type 1 diabetes lead out their lives in as great a way as they would in a life without diabetes. So in this light, I'd like to give you my clinical perspective, as well as personal perspectives around the quantitative data that you've seen so far this morning.

I'd like to begin with this context. It was nearly a hundred years ago, this year, that Banting and Best, and their team in my hometown of Toronto, discovered insulin, and converted type 1 diabetes from a fatal to a treatable condition. I owe everything to that discovery. But if Banting and Best were here with us today, they would be very discouraged by the state of type 1 diabetes in the U.S. and internationally.

People with type 1 diabetes feel isolated.

They carry a high disease management burden. They carry diabetes-related emotional distress, fear hypoglycemia, and fear complications like chronic kidney disease and cardiovascular disease.

In the U.S., more than half of patients with type 1 diabetes are overweight or obese, and it's actually a small proportion who meet the evidence-based guidelines for glycemic control. The estimated average A1c in the population is 8.4 percent, where only 1 in 5 are meeting anyone an A1c of 7 percent or below.

Banting and Best, and we ourselves, need to acknowledge that there is an epidemic of high A1c in the type 1 diabetes population. What do we do to counteract this epidemic of high A1c? We work with physiological insulin and a number of innovations in its delivery, that each have a modest impact, on average, in our patient populations. But we work as clinicians to offer as many options and choices to our patients so that they can individualize their therapy and increase the chance of meeting a target A1c.

For example, insulin pump therapy is transformative for many patients with type 1 diabetes, but our best traditional clinical trial meta-analysis data shows us a mean effective 0.29 to 0.3 percent. There's high burden on the patient and on the education and clinical team to deliver pump therapy. It's associated with an accentuated DKA risk. It's a major complex intervention, and on average, this is the mean estimate of efficacy and similar for continuous glucose data.

You may know of automation of insulin delivery called hybrid closed loop or artificial pancreas, which we have hoped phenomenal improvement, and it does, but the average efficacy is 0.26 percent from our best meta-analyses, pramlintide 0.3 percent A1c benefit associated, though with an accentuation in severe hypoglycemia and also the burden of an additional 3 injections per day.

So if we have a strategy, an oral medication, that can counteract this known biological mechanism of upregulation of sodium

glucose transporters, even people with optimized insulin therapy, and even at the low dose, can have an A1c benefit approximating 0.28 percent, this is of extremely high value. I'm often asked is this 0.28 percent A1c clinically meaningful, and my first strong response is that it compares similarly to some of the incredibly complex interventions that we apply in type 1 diabetes.

Secondly, that A1c reduction is accompanied by salutary glucometabolic factors, a weight reduction, no increase in hypoglycemia, a blood pressure reduction, and a measured increase in patient satisfaction. When we improve A1c through intensification of insulin, for example applying an insulin pump, generally, there is weight gain. If we were to apply pramlintide to have a similar A1c reduction, generally there's an accentuated risk of hypoglycemia.

Could we predict even these small glucometabolic improvements from this low dose that we wish could be the same magnitude as the high dose, could we predict that these smaller effects

could have long-term benefit in terms of meaningful outcomes?

Well, here we can apply the data to the core diabetes model, the Center for Outcomes Research in Switzerland. This is an independent, established, referenced standard disease progression model. It's designed to project long-term health outcomes in diabetes. The type 1 model is derived from the DCCT/EDIC findings that you were referred to earlier, and there's an annual reevaluation of its validity.

Applying the EASE-3 study empagliflozin estimates to a lifelong treatment, we would estimate a 12 percent relative risk reduction for end-stage renal disease, 9 percent for major cardiovascular events, and an increase in life expectancy of 5 months. This is to say that minor glucometabolic benefits are still believed to translate into meaningful lifelong outcomes.

So let me shift to the concern on the risk side of diabetic ketoacidosis. I'd like to go through some key considerations. The first thing

is that there is a background population risk for DKA in the type 1 population, 5 percent. Out of every 100 patients that I follow in my clinic with type 1 diabetes per year, I expect 5 episodes of diabetic ketoacidosis. I know that that centers on the most vulnerable, the low socioeconomic status, younger individuals, highest A1c's, those struggling with self-management.

Whether we introduce SGLT inhibition into this population in the U.S., as has been introduced in Europe and in Japan, we need to do better with preventing DKA.

The second key consideration is that we know about the mechanistic causal relationship between these drugs in DKA. It isn't a stochastic side effect that we're unable to think through as clinicians. We know that there is a shift in metabolism, lower insulin dose, and an increase in glucagon associated with these. It increases ketone production.

We know from historical literature that the prototype from this class, or genetic mutations in

these transporters, are associated with a very benign phenotype of glucose lowering, except in particular situations, like in starvation or with acute illness, infection, surgical stress, or severe insulin deficiency.

We see in our phase 3 program this relationship that shows that it's a component cause, it's neither necessary or sufficient for DKA, meaning we don't need to be on an SGLT inhibitor to have DKA. It's not necessary nor is it sufficient. In all of the episodes of DKA in people on an SGLT inhibitor, there is another identified precipitating cause.

We as clinicians, understanding these mechanisms and these realities, can work clinically through physiological insulin and education to counteract this, as opposed to a side effect that is stochastic for whom the mechanism would not be known. Finally, we've successfully adapted therapies with DKA risk into type 1 diabetes practice, and here I refer specifically to insulin pump therapy, where even recent meta-analysis

demonstrates, at least from the earliest studies, a 5-fivefold odds of increase in DKA.

Well, as a clinical community, knowing that this is important to patients and clinical care, we worked through this risk. We worked with education. We worked to push for safer pumps with alarms and better catheters. We can adapt to a therapy with a known mechanism and an increased risk.

Our FDA colleagues have shown us the current use of SGLT inhibition in the type 1 diabetes population in the U.S. is occurring. Using the U.S. Sentinel pharmacovigilance data set, we know that off-label use is occurring. It's in the high doses, those that are approved and available for type 1 diabetes, and it provides us real-world evidence for increased DKA risk.

I feel very strongly that we need to address this reality. I'm not saying that approval of this type 1 specific dose will completely eliminate off label use, but as a clinician, I need to know that I have that option that has mitigation strategies.

The first mitigation strategy in itself is the low-dose empagliflozin to reduce DKA risk.

Though we didn't see DKA risk in the clinical trial setting, we did see this slight increase through the mechanism of ketosis-related events, and I do not know for certain how this will apply in the real world. So the low-dose approach on its own, though it gives me a lot of confidence, is not enough, and it requires an education program.

Already, there are these exceptionally clear and pragmatic approaches that have been published for mitigation of DKA by specialists and expert consensus groups.

The first step in this education is this concept of patient selection, where in my mind, it's selecting patients at the right time in their type 1 diabetes management, non-pregnant adults adherent to monitoring and who understand physiological insulin administration and the foundation of type 1 diabetes management, who haven't shown recent decompensation like recent

DKA. They're willing to abstain from avoidable risk factors like a very low carb diet, and they understand and can act on ketone testing and a management protocol, testing regardless of a glucose level and holding in certain situations like sick days.

This is not an insurmountable task for a clinician to go through these key principles, and in fact, I feel that this can help with education; that if I review these with every patient and someone doesn't understand the foundation principles of the physiological insulin regimen, or doesn't understand and approach to sick-day management, this is not the right time to consider other therapies. Perhaps later in their diabetes journey would be a time to have a further option like adjunct SGLT inhibition.

The published education tools that exist, some of them are simple, like the STITCH protocol. Others are more prescriptive like the DKA or the STOP DKA protocol out of Canada. They provide key features around patient education and healthcare

provider education, and you've seen aspects of these, and some of them are summarized here.

But I wanted to make two key points from this. The first is around this concept of a wallet card. Now, in clinical practice, I will review with patients symptoms of DKA currently now. If you feel nausea, vomiting, malaise, fatigue, or unwell in any way, and you have an unexpectedly high blood sugar, above, for example, 250, that is a situation to test a ketone currently.

Having this conversation around potentially prescribing empagliflozin 2.5, I would say these same symptoms, but regardless of blood sugar, would be an instance to test. If you wake up in the morning feeling nauseous, regardless of blood sugar, that is a situation to test for ketones. The wallet card provides me with this opportunity for every time that they open up a package of this prescription, month by month and year by year, there's this immediate reminder that I wish we already had in clinical practice. Finally, this dedicated type 1 specific brand enables these

educational measures to be focused on the right population.

Let me conclude. We've heard that we have an epidemic of high A1c in the type 1 diabetes population, and that what we need are options for patients, where currently each innovation has a moderate average A1c benefit. But we hope as individual patients take on these therapies, that they will have greater benefit, more than a 0.28 or 0.29, for example, and those who don't will consider other therapies or consider this therapy at a later phase.

We have a medication here that clearly has a biological effect on reducing A1c. It does this in a similar magnitude to other complex therapies, it's associated with other glucometabolic benefits, and additionally, we can predict a benefit in terms of long-term outcomes.

This dose of the medication changes the risk profile compared to those drugs approved in Europe and in Japan in that the DKA risk was not observed in clinical trials. Though we still believe the

mechanism of action in the real world could increase that risk, we have excellent mitigation strategies: low dose, education material, and a dedicated brand.

With a strong biological rationale except, extensive clinical trial evaluation, and knowledge of this adjusted risk and benefit ratio, I feel strongly committed as a clinician to the fact that we have a unique opportunity to provide patients with an expanded panel of options for successful, individualized therapy of type 1 diabetes. Thank you very much.

Applicant Presentation - Jyothis George

DR. GEORGE: Thank you, Professor Perkins, indeed. We do have an opportunity to add a meaningful option that improves metabolic control without waking and without increasing the risk of hypoglycemia. Almost 2000 patients volunteered their time and effort to make today's presentation possible. I want to thank them for helping address their unmet need. I also want to thank the panel for the opportunity to discuss this proposed

indication today.

All speakers and respondent responders are receiving compensation for the time and expenses. In addition to the speakers you heard from, we have professor Lori Laffel, from the Joslin Diabetes Center and Harvard Medical School, who has extensive experience in diabetic ketoacidosis research; Professor Darren McGuire, cardiologist and professor of internal medicine at UT Southwestern Medical Center, with a career focused on addressing cardiovascular complications in diabetes; and Professor Bernard Zinman from the University of Toronto, a principal investigator for the NIH-funded landmark Diabetes Control and Complications, DCCT, Trial. Thank you.

Clarifying Questions to the Applicant

DR. BURMAN: Thank you very much for the nice presentation.

We will now proceed with qualifying questions to the applicant, and I point out the time. It's about 9:45. We're going to go until 10:10 for the break, and there will be time for

questions later. Please raise your hand or make notice to Commander Bonner, and we'll call on you.

Dr. Everett?

DR. EVERETT: Thank you, and thank you for the interesting and very informative presentation from the sponsor. I was wondering if we could just turn to page or the sponsor's slide number 65. My question has to do specifically with the endpoints' committee's adjudication process for determining whether or not a case was DKA.

In particular, I see that in order to have DKA, you had to have acidosis. My question is did you have to have an ABG that demonstrated acidosis or could an anion gap or a low bicarbonate be sufficient to infer that there was an acidosis?

DR. GEORGE: We did use more than arterial blood gas. Dr. Marquard can walk you through the case definitions.

DR. MARQUARD: According to our charter, pH was the primary differentiator for the assessment of acidosis, followed by bicarbonate and anion gap. Whenever both components were available, the

advice, according to the charter, was to rely primarily, then, on pH.

DR. EVERETT: What I'm driving at is some of the cases that I read, or vignettes that were in the briefing document, noted that a pH could not be obtained, and yet the patient was clearly acidotic, based on their bicarbonate. Would that have been discounted as a non-case of DKA on that basis?

DR. MARQUARD: Evidence of low bicarbonates, together with high ketones, would be according to the charter a certain DKA event.

DR. EVERETT: Okay. That's great. My second question was just mostly concerned with incomplete ascertainment of cases that may be medically serious because they didn't meet the, A, or potentially B, where the overlap between acidosis and DKA symptoms might have been excluded or considered as real DKA or potential DKA cases --

DR. BURMAN: Thank you. Before we go to the next question or comment, I'd like to introduce Ms. Anna McCollister-Slipp, who came in late, and

welcome to the committee as the patient representative.

The next question will be from Dr. Brittain.

DR. BRITTAIN: My question is on slide 57, although it's not about the exposure-response simulation study. It's more about the pattern that we see here in the curves. I'm asking about this one as opposed to the EASE-3 that has the 2.5, but we see kind of the same pattern that there's a pretty big drop right away, and then it kind of starts going away.

Now granted, we see a similar thing going on in placebo, which is I'm sure while you're still getting your big difference against placebo, but given that you only have the 26-week data on the 2.5, and you see kind of the same pattern in both studies, it does sort of make you wonder could the effect be going away over time, and I wonder what you think about that. And I also wanted to say I thought your presentation was great.

DR. GEORGE: Thank you, Dr. Brittain. Dr. Perkins will walk you through why the placebo

and the other amps [ph] are rebounding, because this is a clinical question.

DR. PERKINS: Sure. If I appreciate your question correctly, the first is this idea of the upward drift over time, and then secondly, beyond 26 weeks, what could be envisioned at one year. The first thing, I would like to highlight a couple of design aspects of the trial.

The first is that there was this insulin optimization phase, and during that insulin optimization phase, prior to randomization, there was a 0.5 percent A1c drop. This is a big deal in type 1 diabetes, to have a 0.5 percent A1c drop, and I would have imagined that the natural history after this is for a gradual, at least partial return because that is what we see clinically.

The counterfactual situation we're offered is the placebo group, and it shows exactly that. So mostly they're maintaining some, but there is a bit of a drift in A1c. That gives us the counterfactual natural history of what happens after insulin optimization. What we see with the

medications, even the 2.5-milligram dose, is a further drop, but that same counterfactual natural history of a slight increase in A1c. I guess that's my first point.

Around the durability to a year, here I'd make two points. One is the observations with the higher doses, 10 and 25 milligrams. There is some loss of that durability, but there's still a substantial difference between placebo at one year, at 52 weeks. With the 2.5-milligram dose, we don't have the liberty of knowing that's 52 weeks, but from modeling studies and understanding of the pharmacokinetics and pharmacodynamics up to a year, we would estimate a durable effect.

I hope that sufficiently answers the question.

DR. GEORGE: Thank you, Professor Perkins. If I may add a couple of points to your question, first, like Professor Perkins said, our aim was to look at what the efficacy of empagliflozin would be on top of what patients and physicians could manage, and the bounce back reflects that.

The other point I would just like to add is that although, as you said, there is a tendency for A1c to go up over time, even in the treatment, as Dr. Marquard presented earlier, other efficacy markers show sustained effects. This is why at the end of the day, we believe it's important that patients and physicians discuss this and come to a personalized management choice themselves.

DR. BURMAN: Thank you. Dr. Wang?

DR. LOW WANG: Cecilia Low Wang. Thank you. I also had concerns about the adjudication categories, especially the unlikely DKA but ketosis, after reading the different vignettes. Because of that, I wondered because it's difficult to go from the EASE-3 safety data, 26 weeks to 52 weeks and beyond, I wonder if you have EASE-2 data, for the higher doses, at 26 weeks for the rate per hundred patient-years for certain or potential DKA as well as ketosis. I didn't see that in the documentation.

DR. GEORGE: Your question is about looking at the broadest definition of not just certain

potential DKA but also adding the ketone-related events to that, and whether we have that for 10 and 25 weeks, 25-milligram doses; correct?

DR. LOW WANG: Exactly; so a broader definition, as well as the earlier time point at 26 weeks to try to figure out what the safety data from EASE-3 means.

DR. GEORGE: Thank you. We do have the analysis for the full trial ready to hand, but I'm not sure we have the analysis at 26 weeks ready for you to look at, but that is something that we can certainly try to do over the lunch break and bring it back to you.

Dr. Everett also raised the question about adjudication that we haven't fully answered, so if I may, Mr. Chairman, try to answer that in two ways. First, I would like Dr. Marquard to go through the clinical case definitions we used. We understand it's complex. Our aim with the adjudication process was, at 2-fold, one, to cast as wide a net to capture all events, and two, to have a range of definitions that go beyond certain

DKA. We understand it's complex, so please allow us to walk through the case definitions.

Dr. Marquard, please?

DR. MARQUARD: Could I please have slide CC-65? Slide 1 up, please. Please allow me to provide some additional context, especially around the unlikely category. For certain DKA, we basically needed confirmation of acidosis and ketosis. For unlikely, we basically needed confirmation that the patient had either no acidosis or no ketosis, because if there's evidence that there is normal pH or normal ketones, this event would not be a diabetic ketoacidosis, according to the general concept of diabetic ketoacidosis.

This is why we also introduced the potential category because the potential category combines or basically captures events where only pH and symptoms are available or where we only have ketones and symptoms. And since we had patient ketone monitoring in our studies and they reported this in the e-diaries, we had a lot of these

readings that were reported together with symptoms that were sent to adjudication, and were basically a big part of the outcome potential ketoacidosis.

We also introduced the subcategory ketosis. Because of the high sensitivity of the charter, we expected that there could be a high number of unlikely DKA events. Therefore, we introduced the subcategory unlikely but ketosis to better differentiate this outcome.

Indeed, there are cases with clear evidence that a pH value was normal, however, ketones elevated in these events were, according to the charter, unlikely DKA events but ketosis. The adjudication committee has adjudicated most of these events, also according to the charter, however, they could always bring in the clinical judgment.

DR. GEORGE: The one additional concern was about sensitivity and specificity. If I may ask Professor McGuire to make a brief comment about the general challenge that we faced in that adjudication with sensitivity and specificity.

DR. McGUIRE: Good morning. Darren McGuire from University of Texas Southwestern Medical Center in Dallas. I'm a cardiologist and clinical trialists, having spent 25 years working with a focus on diabetes and cardiovascular disease and outcomes. I have no equity interest in the company and do not stand to benefit from the results of this meeting.

I think just to bring home, as we began to dive in, and we both throughout the day, I'm sure, are digging down deep into these DKA events and the classification thereof, I think it's important to remember the basic tenants of adjudication, one of the key features of adjudication is it levels the playing field. It inevitably exchanges sensitivity for specificity.

It is very uncommon for an event to undergo adjudication and be refuted. I mean, it is common for an event to be refuted; it is very uncommon to be elevated to a higher degree of classification. The key important point of that central adjudication is that it's done blinded.

So to do post hoc analyses of unblinded data, it does yield incremental information and clarifies some cases that were on the border zone, but I think we do have remember, as imperfect as charter definitions are, they do even the playing field, especially when it's done in a blinded fashion.

DR. BURMAN: Thank you.

Dr. Yanoff, you had a comment as well from the FDA?

DR. YANOFF: Yes. I just wanted to say that I believe in our presentation, or at least in the backup, we have the analyses that Dr. Low Wang requested. No one may need to give up their lunch hour to do those.

DR. GEORGE: Thank you, Dr. Yanoff.

DR. BURMAN: Thank you. Dr. de Lemos?

DR. DE LEMOS: I'm wondering what else the sponsor has for DKA. We're sort of being asked to evaluate safety here on essentially what's a hundred person-years of follow-up for DKA. Was there no plan for open-label extension with the 2

and a half or even the higher doses? Was there modeling done in the second study for this DKA outcome like it was for A1c?

What else can you tell us about, beyond a hundred person-years of follow-up, that gives us confidence that A, it's no different from placebo, and B, that the rate of DKA is materially lower than the two higher doses?

DR. GEORGE: To give you confidence that the lower dose indeed provides a materially lower risk, we have done modeling, as you implied. Dr. Valerie Nock can present that information for you.

DR. NOCK: Good morning. My name is Valerie Nock. I'm a team lead for pharmacometrics with Boehringer Ingelheim, and in that role responsible for the empagliflozin development program. Specific to your question whether or not we performed modeling for DKA events, we were not able to conduct such an analysis. The reason is that DKA is an event that is not only driven by empagliflozin exposure, but by a lot of precipitating factors.

Now, for patients who experienced a DKA event, we do know of those factors. It might be pump failure or it might be an infectious disease. However, for patients who had a pump failure on infection, we did not capture this information, so we could not rely on a reference group.

As we were not able to model DKA, what we conducted was a exposure-response analysis for blood ketones, and I'm happy to share those results with you. Slide 1 up, please. Depicted on this slide is the exposure-response analysis for blood ketone values after 26 weeks of treatment.

Over the steady-state AUC, that is the area under the concentration time curve, a measure for empagliflozin exposure. And as shown here, for typical subject, we see an exposure-dependent increase in blood ketone levels. However, it is important to note that, on average, the increase is of minor magnitude and far away from the criteria that defines a ketosis, which is 1.5 millimoles per liter.

DR. BURMAN: Thank you. Dr. Pai?

DR. PAI: My question, again, is kind of related to the exposure-response relationship. If you go to slide 60, what you see is a simulation after 52 weeks, showing the same effect, relative to placebo. Could you clarify to us, because this is a placebo-corrected event, compared to baseline, what is the change at that dose level? Are we seeing a negative 0.29 because placebo is going up or is it a true difference?

DR. NOCK: The reason we see the same effect after 52 weeks, as well as 26 weeks, is because we describe it as placebo-corrected change from baseline.

Slide 1, please. As you've previously seen in the core presentation, not only the placebo group shows an increase in A1c over time after the first 4 to 12 weeks of treatment, but also empagliflozin 10 and 25 milligram. And as they go up in parallel, and we describe this and capture this with our model, the predicted placebo-corrected change from baseline is sustained over time.

DR. PAI: Just to clarify that again, at 52 weeks, what is the absolute change in placebo compared -- what is the -- basically what I'm getting at, is it zero, and is placebo at 29 percent; 0.29 for example, and that Delta is now negative 0.29?

DR. GEORGE: Dr. Pai, that is a question that we do not have the answer for. Again, that's something that we can come back to at lunch. But from a clinical perspective, like Professor Perkins put it together, these small [indiscernible] decimals are probably not that relevant. Most of our patients, we talk about 7 point something or 8 point something. But certainly we will try our best to bring that information back to you over lunch to see what was the difference between placebo and then in the model at one year.

DR. BURMAN: Thank you. We have about five more minutes. Dr. Yanovski?

DR. YANOVSKI: Thanks. I have two relatively quick questions. First, if you look at figure 18 in the document that you sent us, which

is the time course of ketone-related events per patient --

DR. GEORGE: slide 1 one up, please.

DR. YANOVSKI: -- these are the data through the EASE-3 trial. It would seem that the ketone-related events are separating between placebo and empa 2.5. Have you modeled this to a full year, and how does that compare with the kind of rates that might make us worried about the chances of ketone-related events?

DR. GEORGE: As you state, there is a tendency for empagliflozin 2.5 milligram to have a higher degree of ketone- related events. This is largely driven by ketosis with values more than 1.5. We certainly can put this into context with the other ketone-related analysis.

Dr. Schorling, if you could come to the podium to do that for us, please.

DR. SCHORLING: Could I call slide CC-17? Slide 2 on, please? Here we are looking at, in the first row, ketone-related events. Ketone-related events analysis is the most comprehensive analysis,

which consists of all events that were adjudicated as sudden DKA, potential DKA, unlikely DKA but ketosis, and, in addition, all elevated ketone values above 1.5 millimoles per liter.

That's the majority of the events in this analysis, ketosis events. These events were managed by patients at home. Based on this most comprehensive analysis, the rate ratio was 1.65, which is less than half of the increase with the higher doses.

DR. BURMAN: Thank you. Ms. McCollister, we have a few minutes for your question.

DR. YANOVSKI: Can I ask my second question? May I?

DR. BURMAN: Sure.

DR. YANOVSKI: My second question, really, is related. If ketone measurements are probably very key in avoiding DKA events in these trials, can you show us any data on the rate of use of ketone measurements in the trials through an entire year? Do the people stop measuring their ketones with time, and could that potentially be something

we would be worried about?

DR. SCHORLING: We saw that patients adhered to ketone monitoring quite well in our trials. Approximately 98 percent of patients had measurements. I can show you the slide.

Slide 4 on, please? The bottom line shows the total number of measurements in patients, that treatment arm, first in these three, and then four across two trials for the higher dose. Based on this number, 22,000 for 2.5 milligram, for example, this number corresponds with 3 to 4 measurements per week. Our recommendation was to measure 2 to 3 times a week, so there was good adherence to our recommendations.

DR. GEORGE: Dr. Yanovski, if I also could clarify your question, I believe there was a concern about is there reduction [indiscernible] in ketone adherence over time. That's not something that we observed. We have additional data to share with you if needed.

DR. BURMAN: Thank you. I apologize. Dr. Lellock, the last question, quickly please.

I'm sorry. Ms. Lellock?

DR. LELLOCK: I've had diabetes for almost 30 years, and I commend the recognition of our unmet needs. My biggest question is, for patients who have met goal with intensive insulin therapy, do you still find that this is a drug for them, based on the secondary endpoints?

DR. GEORGE: That is a great question. Our indication that we seek today is for glycemic control, and your question is about would there be other benefits for patients who are already at target. I can only refer back to what Professor Perkins said earlier. It truly is between that patient and that physician, how they would choose these different tools in the toolkit for that particular patient.

DR. BURMAN: Last question, quickly, Rita Kalyani?

DR. KALYANI: Thank you for that nice presentation. My question relates to slide 71, measures to minimize DKA risk. The point-of-care device to measure blood ketones, unlike

point-of-care measures to measure blood glucose, are not widely available yet. I wonder if you could talk a little bit more about what was done in the trial.

It looks like during the first month, participants measured every day, and then after that, 2 to 3 times a week. Given what seems to be a relatively high requirement from the patients, could you talk a little bit more about translation into real-world board settings?

DR. GEORGE: Yes. I would like to ask Professor Lori Laffel to put that into clinical context for us.

DR. LAFFEL: My name is Dr. Lori Laffel. I am a pediatric endocrinologist and clinical investigator at the Joslin Diabetes Center and a professor at Harvard Medical School. I have no equity in the company. I will not benefit at all from an FDA decision today.

I do have substantial experience in managing young persons with type 1 diabetes for over 30 years. I take care of pediatric adolescent and

young adult patients, many patients of whom would fall within the age range for which the sponsor is seeking approval, ages 18 to 30, or so.

I have been studying and writing guidelines for sick-day management in the setting of type 1 diabetes for more than two decades. We have been advocating for blood ketone monitoring, and indeed that has become the standard of care, as advocated by the American Diabetes Association, as advocated by international organizations, including the International Society of Pediatric and Adolescent Diabetes.

Checking blood ketones is fundamental at the diagnosis of type 1 diabetes. Patients are taught and prescribed a blood ketone monitor, as well as taught sick-day rules. This is reinforced at the time of any illness, and it is reinforced anytime a new prescription for blood ketos strips is written, and it is timely to reinforce it annually when flu shots would be administered.

We did indeed perform a study, now about a dozen years ago, that compared checking blood

ketones with urine ketones in a randomized-controlled trial, and we actually demonstrated that 50 percent more of the participants, which were pediatric adolescents and young adult patients, randomized to blood ketone monitoring, were successful in checking blood ketones over urine ketones at the time of illness. More than 9 out of 10 adhered in this study to blood ketone monitoring, where barely 6 out of 10 did in the urine ketone monitoring group.

I do recognize the need to ensure coverage for blood ketone monitors and blood ketone monitoring strips, and I as a clinician advocate for such prescriptive coverage, and it indeed is potentially cost saving. And in that RCT that I published about a dozen years ago, we demonstrated a 50 percent reduction in costly hospitalizations and emergency department assessments, which would be cost saving compared to the cost of blood ketone meters and blood ketone strips.

DR. GEORGE: Thank you, Professor Laffel. If I may just add one sentence, Mr. Chairman, to

that comment, to Dr. Kalyani's question about continuing use in the real-world setting. As a sponsor, we do propose to provide patients with starter kits and health systems to make the information and tools accessible to patients.

DR. BURMAN: Thank you very much for the sponsor and for the questions. We're going to take a break now until 10:25 when we'll reconvene. Please remember not to discuss any issues during the break.

(Whereupon, at 10:14 a.m., a recess was taken.)

DR. BURMAN: Thank you. We'll now begin with the FDA presentation.

FDA Presentation - Mahtab Niyyati

DR. NIYYATI: Good morning. I am Dr. Mahtab Niyyati from the Division of Metabolism and Endocrinology Products. I'll be presenting a general overview of the empagliflozin clinical development program. Dr. Justin Penzenstadler will then discuss the clinical pharmacology; Dr. Roberto Crackel will present the statistical efficacy

assessment; and Dr. Shanti Gomatam will present the statistical safety assessment of diabetic ketoacidosis.

I will conclude the FDA presentations by presenting a summary of safety and efficacy for the empagliflozin 2.5 milligram dose. Please note that in the FDA talks, we will sometimes refer to empagliflozin as empa.

The applicant conducted two phase 2 studies relevant to empa 2.5-milligram dose called EASE-1 and J-EASE-1, and two phase 3 studies, EASE-2 and EASE-3. The applicant originally designed the empa type 1 clinical program with the objective of registering the same doses as approved for type 2 diabetes, the 10-and 25-milligram once daily.

During communications with the agency, the FDA raised concerns that doses approved but type 2 may not be optimal in the type 1 population due to safety concerns specific to patients with type 1 diabetes and recommended exploration of a lower dose. While the applicant did include a lower dose, it was only in one of the phase 3 trials,

EASE-3. Therefore, to support efficacy, the applicant also performed clinical trial simulation based on exposure-response analyses using the EASE-2 population.

You're already familiar with the design of the phase 3 studies. Points worth emphasizing are that in EASE-3, the continuous glucose-monitoring data was capture in about 20 percent of patients over 4 periods, each 14 days in duration. Both phase 3 trials included an insulin optimization period that lowered the baseline HbA1c from the time of screening.

In addition, the randomized patients were highly selected, which may not always happen in the real world, even with the best possible instructions in the prescribing information. EASE-2 had a similar design to EASE-3. The differences were the duration of the study and the doses studied. EASE-2 did not study the 2.5-milligram dose.

The baseline demographics of patients in the empa 2.5-milligram group compared to placebo were

generally balanced. The mean age was about 42.5 years old. The mean HbA1c was 8.15 percent. Mean body weight was about 81 kilograms. Mean BMI was 28 kilogram per meter squared. At baseline, subjects were normotensive.

In this trial, the clinical benefit evaluated was a reduction in HbA1c after 6 months of treatment. The applicant evaluated additional secondary endpoints of plasma glucose less than 54 milligram per deciliter and/or severe hypoglycemia, body weight, total daily insulin dose, and systolic and diastolic blood pressure.

A reduction in severe hypoglycemia would be viewed as an important clinical benefit. Other definitions of hypoglycemia have uncertain significance in the setting of evaluations of comparative effectiveness or safety. Body weight and blood pressure reduction may be viewed as clinical benefits for some patients. Other endpoints such as time and range may be valued by patients, but we're not aware of data that time and range is a surrogate for long-term outcomes beyond

what HbA1c can already tell us.

The applicant also looked at total daily insulin dose as an efficacy endpoint in this program. We recognize the desire of patients to lower insulin dose. However, in the specific setting of using SGLT2 inhibitors as an adjunct to insulin in the type 1 patients, it's unclear if insulin dose reduction should be a goal of treatment because it's linked to an increase in the risk of DKA.

As for safety assessment, the applicant paid special attention to safety issues that are known to be associated with the product when used in type 2 patients. All other events were collected routinely. DKA, severe hypoglycemia, and hepatic events underwent blinded independent adjudication. Patients were instructed to reduce insulin when starting study drug. Insulin dose changes were individualized, and investigators and patients were relied on to make their own decisions.

Next, Dr. Justin Penzenstadler will discuss the clinical pharmacology findings of the empa

2.5-milligram dose.

FDA Presentation - Justin Penzenstadler

DR. PENZENSTADLER: Hi. My name is Justin Penzenstadler, and I'm with the FDA Office of Clinical Pharmacology. I will present the clinical pharmacology of empagliflozin in type 1 diabetes.

On the screen is the outline of my presentation. First, I will discuss the design and results of the two phase 2 studies, EASE-1 and J-EASE-1. Then I will discuss the results from these studies, focusing on key biomarkers and how they provide supportive evidence of efficacy for the 2.5-milligram dose.

Secondly, I will address the modeling and simulation results submitted by the applicant, which was proposed as confirmatory evidence. In this exercise, data from EASE-1 and EASE-2 were modeled to provide an estimate of HbA1c reduction for the unstudied 2.5-milligram dose.

The FDA conducted sensitivity analyses to confirm the robustness of this exercise as supportive evidence. I will conclude my

presentation with a clinical pharmacology perspective on DKA, discussing the proposed mechanism of SGLT2, induced ketoacidosis, and summarizing the observed data on insulin dose and plasma ketones from EASE-3.

The applicant conducted two PK/PD studies in type 1 diabetic patients, EASE-1 in Caucasian patients and J-EASE-1 in Japanese patients. These studies were randomized, placebo-controlled, double blind, in parallel group studies with placebo, empagliflozin 2.5, 10, and 25-milligram groups. The primary objective in both was to assess PK in 24-hour urinary glucose excretion, also abbreviated as UGE.

In addition, HbA1c was collected at baseline and at 4 weeks. Both studies included an open-label run-in period preceding randomization, however, unlike the phase 3 studies, there was not an insulin optimization period. Instead, the 28-day randomized treatment period was split into two phases. During the first phase, patients were hospitalized and kept on stable background insulin

for one week. During the second phase, insulin was adjusted to achieve optimal glycemic control for weeks 2 to 4.

Next, I will discuss the pharmacodynamic results from these studies. This is a graph of the 24-hour urinary glucose excretion on the Y-axis versus plasma empagliflozin levels on the X-axis. For reference, the vertical dash lines are centered on the mean plasma levels for the 2.5- and for the 10-milligram dose.

Empagliflozin shows exposure related increase in 24-hour urinary glucose excretion in subjects with type 1 diabetes shown by the top curve depicted in blue, the 2.5 milligram empagliflozin dose elicits an appreciable effect on 24-hour glucose excretion, more than three-quarters of the 10 milligram once daily dose.

We have also included exposure-response data for type 2 diabetics, depicted in the lower curve in red. We note a consistent exposure-response relationship for UGE between the two populations. On the next slide, we will cover the short-term

HbA1c reductions observed in the phase 2 studies.

Although HbA1c reduction was not a primary endpoint, both studies reported a decrease in HbA1c with the 2.5-milligram dose. EASE-1 reported a decrease in HbA1c of 0.35 points at 28 days, while J-EASE-1 reported a decrease in HbA1c of 0.20. Overall, UGE and HbA1c data from these studies indicate that the 2.5 milligram once daily dose is associated with pharmacodynamic responses that are differentiable from placebo.

Now we will switch gears and briefly discuss the modeling approach used to generate supportive evidence of efficacy for the 2.5-milligram dose. In this approach, pharmacokinetic, demographic, and HbA1c data from the phase 2 study, EASE-1, and phase 3 study, EASE-2, were used to develop an exposure-response model.

The applicant used an informative Bayesian prior from an exposure-response analysis in type 2 diabetic patients to help inform the relationship between exposure and HbA1c reduction. The EASE-2 data was then fed into the model and used to

predict the results of a hypothetical 2.5-milligram arm.

Independent data from EASE-3 was used to evaluate the ability of the model to reproduce observed study results at different doses and different time points, so called external validation. It is not clear if the use of an informative Bayesian prior from a different population and a different endpoint is appropriate, therefore, the FDA conducted exploratory analyses without it.

Here we present the conservative 95 percent lower confidence bound estimate so called, by us, the worst case estimate of placebo adjusted HbA1c reduction from the modeling exercise. The prediction for this model is a 0.23 point reduction in HbA1c with a 95 percent confidence interval of 0.05 to 0.4.

We routinely estimate the effect size for use and benefit-risk analysis, however, this is usually associated with information about the formal statistical test such as a p-value.

Modeling produces a similar estimate of the effect size, but for a dose that is not directly tested, and the confidence intervals and p-values associated with these model-based estimates should be considered descriptive. Overall, we believe this model provides supportive evidence of the effect size for the 2.5-milligram dose independent of EASE-3.

Now, we will discuss the clinical pharmacology perspectives on diabetic ketoacidosis. Diabetic ketoacidosis is the most important safety issue pertaining to the use of SGLT2 inhibitors, including empa, among type 1 diabetic patients. DKA occurs due to insulin deficiency, either relative or absolute, and subsequent ketogenesis.

In general, SGLT2 inhibitors increase the risk of DKA, and this risk is dose dependent. The mechanisms are likely related to both indirect effects through insulin dose reduction and volume contraction and direct effects through ketogenesis, as shown in this slide.

Through urinary glucose excretion, SGLT2

inhibitors cause a lowering in plasma glucose levels, which leads to a rebound reduction in insulin dose. This leads to an increase in lipolysis and ketogenesis in the liver. Additionally, SGLT2 inhibitors increase the renal resorption of ketone bodies, thereby increasing ketone levels in the plasma, while resulting in a reduced ketone level in the urine. Finally, SGLT2 inhibitors decrease sodium resorption, resulting in volume depletion, which may worsen the risk for DKA.

A shift from carbohydrate metabolism to fatty acid metabolism is accompanied by an increase in plasma ketones. Beta-hydroxybutyrate, or BHB, is the most abundant of the three ketone bodies created by the liver, followed by acetoacetate and acetone. The mean BHB and standard error from EASE-3 is shown in this slide. There is a dose-dependent increase in BHB with the highest change apparent at week 12. Note, the reference range is different between institutions and laboratories, but is generally less than 0.4 to

0.6 millimoles per liter.

Upon discontinuation at 26 weeks, the BHB levels return to baseline within 2 weeks. We note a small dip in the BHB levels during the 6-week insulin optimization period among all arms, which likely reflects a shift towards increased carbohydrate utilization for more optimally dose insulin.

The increase in BHB post-randomization indicates a shift towards reduced carbohydrate utilization and subsequent lipolysis and fatty acid oxidation. We note similar dose-response patterns in routinely ordered plasma ketone labs. The increases of BHB under treatment may reduce the capacity to compensate to exogenous insults in carbohydrate metabolism such as missed meals, missed insulin doses, or sick days.

In addition, empagliflozin treatment caused a sustained decrease in concomitant insulin use. Reductions in insulin were dose dependent, with an average decrease of approximately 7 and a half percent in the 2.5-milligram arm and 10 to 15

percent in the 10- and 25-milligram arms. We note that a maximal or near maximal decrease was observed at 1 week post randomization, which was the earliest time point in this analysis.

Overall, the clinical pharmacology information in this application provides corroborating evidence of efficacy for the 2.5-milligram dose. The BHB and insulin data from EASE-3 indicates empagliflozin treatment causes a shift away from carbohydrate metabolism.

Finally, we observed dose-response relationships for all pharmacodynamic endpoints, including those predictive of efficacy such as UGE, HbA1c, and safety, such as BHB, plasma ketones, and insulin reductions. In all cases, the 2.5-milligram dose elicited an effect intermediate between placebo and the higher doses of these biomarkers.

Now I welcome Dr. Roberto Crackel to discuss the statistical efficacy results.

FDA Presentation - Roberto Crackel

DR. CRACKEL: Good morning. I'm Dr. Roberto

Crackel, the statistical reviewer from the FDA. I will present the statistical assessment of efficacy from empagliflozin 2.5 milligrams in comparison to placebo in the EASE-3 study. Here's the outline of my presentation. I will first give an overview of the trial, then discuss the efficacy analyses, and results for the primary and secondary endpoints. Finally, I will give concluding remarks.

The EASE-3 trial was a randomized, 26-week, double-blind, parallel group, placebo-controlled multicenter study. In total, there are 975 subjects who were equally randomized and treated to empagliflozin 25, 10, and 2.5 milligrams and placebo. There are 482 subjects randomized and treated to empagliflozin 2.5 and placebo, where there are 241 subjects in each arm.

The primary endpoint was change in HbA1c from baseline to week 26. Secondary endpoints include rate of symptomatic hypoglycemic events with confirmed plasma glucose less than 54 milligrams per deciliter and/or severe hypoglycemic events, confirmed by adjudication per

patient year from week 1 to week 26; change in body weight from baseline to week 26; change in total daily insulin dose from baseline to week 26; and change in systolic and diastolic blood pressure from baseline to week 26.

Another endpoint of interest is the proportion of patients with HbA1c less than 7 percent at week 26. Please note that secondary endpoints for empagliflozin 2.5 were not included in the testing structure. Therefore, analysis results for secondary endpoints are presented for exploratory purposes only.

I'll now discuss the proposed analysis for the primary endpoint. The sponsor's primary analysis model was the mixed model repeated measurements or MMRM. The model included baseline HbA1c and baseline eGFR as linear covariates, and baseline preexisting insulin therapy, treatment, visit, visit by treatment interaction, and baseline HbA1c by visit interaction as fixed effects.

The analysis was performed on the full analysis set, which was defined as all randomized

subjects who were treated with at least one dose of study drug who had a baseline and at least one on-treatment HbA1c measurement. Further, only data while patients were on treatment were used.

The FDA preferred analysis is using an Ancova model after missing data are imputed with a washout method. All available data from the treated set, defined as all randomized subjects who were treated with at least one dose of study drug, should be used. For the washout methodology, missing week 26 measurements for patients on empagliflozin were imputed based on placebo completers.

For each complete data set, an Ancova was run using prespecified factors and covariate. Rubin's rule was then applied to synthesize results to obtain an estimate of the treatment effect. This table summarizes data capture for the primary endpoint. We see that 3.3 percent of patients had missing week 26 data on empagliflozin 2.5 and 7.9 percent of patients had missing week 26 data on placebo.

I'll now discuss efficacy results based on the FDA preferred analysis. This table presents the results on change in HbA1c from baseline at week 26. The mean baseline HbA1c was 8.15 percent on empagliflozin 2.5 and 8.19 percent on placebo. The reduction in HbA1c compared to placebo is 0.26 percent, which is similar to a reduction of 0.28 percent, based on the sponsor's primary analysis.

The result on HbA1c is statistically significant since the 95 percent confidence interval for the difference excludes zero. However, please note that the reduction of 0.26 percent in HbA1c change is mainly due to an increase of 0.2 percent on placebo. The decrease on empagliflozin 2.5 is only 0.05 percent.

These plots depict the change in HbA1c and total insulin over time, based on patients with complete data. We see that for HbA1c, between baseline and week 4, empagliflozin 2.5 and placebo decrease; between week 4 and week 18, empagliflozin 2.5 and placebo increase; and between week 18 and week 26, empagliflozin 2.5 and placebo are fairly

stable.

For total insulin, there was a slight decrease of approximately 1 unit at week 26 from baseline in the placebo arm. For empagliflozin 2.5, there was a decrease between baseline and week 4 and remains generally steady after week 4. There was approximately a 5-unit reduction in total insulin on empagliflozin 2.5 at week 26 from baseline.

This table describes the analysis results for adjudicated severe hypoglycemic events between week 1 to week 26. In comparing the number of patients with at least one severe hypoglycemic event between empagliflozin 2.5 and placebo, the adjusted odds ratio is 0.357. We note that there was one patient on empagliflozin 2.5 with 7 events.

The adjusted event rate ratio comparing empagliflozin 2.5 to placebo is 0.846. The confidence intervals for both the odds ratio and event rate ratio include 1, therefore, we conclude that empagliflozin 2.5 offers no benefit in reducing severe hypoglycemic events.

This table describes the analysis results from investigator-reported symptomatic adverse events with confirmed plasma glucose less than 54 and/or adjudicated severe hypoglycemic events between week 1 to week 26. In comparing the number of patients with at least one event between empagliflozin 2.5 and placebo, the adjusted odds ratio is 0.936.

We observed a difference of 380 events between empagliflozin 2.5 and placebo over week 1 to week 26. This difference is mainly due to an imbalance in prerandomization hypoglycemic event rates. Pre-randomization hypoglycemic event rates were estimated from the number of events occurring 28 days prior to randomization.

The mean pre-randomization rate for placebo was 1.26 events per 30 days compared to 1.05 for empagliflozin 2.5. If we multiply the difference in pre-randomization event rates by 241 patients and 26 weeks, this will result in an expected difference of 300 events. This is why adjusting for pre-randomization hypoglycemic event rate in

the model yields similar event rates for empagliflozin 2.5 and placebo over week 1 to week 26.

The adjusted event rate ratio comparing empagliflozin 2.5 to placebo is 0.94. The confidence intervals for both the odds ratio and event rate ratio include 1. Therefore, we conclude that empagliflozin 2.5 offers no benefit in reducing symptomatic adverse events with confirmed plasma glucose less than 54 and/or adjudicated severe hypoglycemic events.

As I mentioned earlier, secondary endpoints from empagliflozin 2.5 were not included in the testing structure, therefore, analysis results for body weight and blood pressure presented in the next few slides are for exploratory purposes only.

This table presents the results on body weight. The mean baseline body weight was 81.39 kilograms on empagliflozin 2.5 and 80.92 kilograms on placebo. The reduction on body weight compared to placebo at week 26 is 1.77 kilograms. The 95 percent confidence interval for the difference

excludes zero.

This table presents the results on systolic blood pressure. Please note that patients were normotensive at baseline. The mean baseline systolic blood pressure was 123.48 millimeters of mercury on empagliflozin 2.5 and 120.63 millimeters of mercury on placebo. The reduction in systolic blood pressure compared to placebo at week 26 is 2.01 millimeters of mercury. The 95 percent confidence interval for the difference excludes zero.

This table presents the results on diastolic blood pressure. The mean baseline diastolic blood pressure was 75.19 millimeters of mercury on empagliflozin 2.5 and 74.7 millimeters of mercury on placebo. The reduction in diastolic blood pressure compared to placebo at week 26 is 0.35 millimeters of mercury. However, since the 95 percent confidence interval for the difference includes zero, we conclude that empagliflozin 2.5 offers no benefit in reducing diastolic blood pressure.

This table presents the number of patients achieving treatment goal of HbA1c of less than 7 percent at week 26. There were 14 patients achieving goal on empagliflozin 2.5 and 4 patients on placebo. While all 4 responders on placebo began with HbA1c greater than 7 percent at baseline, we note that of the 14 responders on empagliflozin 2.5, 2 patients began with HbA1c less than 7 percent at baseline, one of whom experienced an increase at week 26.

In conclusion, empagliflozin 2.5 resulted in a statistically significant reduction of 0.26 percent in HbA1c change from baseline at week 26 compared to placebo. However, this reduction of 0.26 percent is mainly due to an increase of 0.20 percent in HbA1c on placebo. The decrease on empagliflozin 2.5 is only 0.05 percent.

There were numerically significant decreases in body weight and systolic blood pressure for empagliflozin 2.5 compared to placebo. However, these endpoints were not prespecified in the testing structure. Further, there is no benefit

from empagliflozin 2.5 in reducing hypoglycemic events.

I now welcome back Dr. Niyyati to the podium to discuss DKA assessments.

FDA Presentation - Mahtab Niyyati

DR. NIYYATI: DKA is an acute life-threatening complication of diabetes that can lead to severe consequences and can be fatal. While all type 1 patients are at risk of DKA, SGLT2 inhibitors generally further increase that risk.

The applicant utilized multiple ways to identify possible DKA events. One way was by capturing investigator-reported DKA as documented in the electronic case report forms. Another way was through a search of the adverse event database by using predefined MedDRA preferred terms, indicative of ketoacidosis or acetonemia.

The applicant also captured BHB values less than 1.5 and greater than 3.8 millimoles per liter accompanied by symptoms suggestive of ketoacidosis or hospitalization, as well as any BHB value equal or greater than 3.8 millimoles per liter from the

lab or the patient's e-diary. It's important to note that the applicant categorized asymptomatic BHB values between 1.5 and 3.8 millimoles per liter as ketosis, and these events were not to be sent for adjudication.

In order to adjudicate cases of DKA, the applicant created categories based on a prespecified set of criteria. Possible DKA events were to be adjudicated in one of these categories. While this may be a reasonable approach for categorizing events in a clinical trial, this may not be how DKA is experienced in the real world.

Multiple DKA prevention strategies were implemented to prevent DKA. Patients were selected who were able to manage their insulin regimen and comply with study procedures such as ketone monitoring. All patients received a point-of-care device capable of measuring blood glucose and BHB.

The investigators were to educate the patients on the risk of DKA. The patients were instructed not to reduce their insulin dose below the investigator's recommendations. Patients were

instructed to test their ketones in case of any symptoms of ketoacidosis irrespective of the glucose value or in case of repeated elevated blood glucose without explanation.

Patients were to be reminded about signs and symptoms of ketoacidosis, the interpretation of ketone values measured via the meter, and appropriate actions to take in the event of increased ketone levels. If ketone levels were elevated, patients had to either follow the investigator instructions or contact the site. Patients were instructed to refer to the investigator and/or to hospital in case of a blood ketone more than 1.5 millimoles per liter, and the investigator had to ensure appropriate tests were performed in case of a suspected DKA.

Patients were reminded about appropriate management of their diet and physical activity, including a reminder to maintain adequate daily fluid intake to avoid dehydration. They were to be reminded about the importance of following a sick-day management plan and corresponding insulin

adjustments should they become unwell during the trial. Extreme diets were to be avoided.

During the conduct of the trial, an additional information card was given to patients to explain the potentially atypical presentation of DKA with the use of SGLT2 inhibitors. Patients were advised to present this card to healthcare providers when appropriate.

Despite the intensive monitoring and prevention strategies implemented in the program, a patient randomized to empa 25-milligram died during the study as a result of DKA. The patient was a 28-year-old female who on study day 107 was evaluated by the investigator for flu-like symptoms, fever, and an elevated BHB of 4.6 millimoles per liter. Of note, this event was eventually adjudicated as unlikely ketoacidosis but ketosis.

The next day, blood glucose was 96 milligram per deciliter. BHB was 2.1 millimoles per liter. The investigator told her to keep controlling blood glucose and did not stop the study drug. There is

no documentation of any further interaction between the patient and the investigator after this point.

She developed severe vomiting and a BHB of 6.3 millimoles per liter, and went to the emergency room. Blood glucose was 190 milligram per deciliter. The patient didn't inform the emergency room about the high BHB levels or participation in the study, and the emergency room did not measure ketones.

In the emergency room, she was diagnosed with sinusitis. She was treated with antiemetics, IV fluids, and antibiotics. She was discharged home. Later, she developed vomiting, abdominal pain, a blood glucose of 300 milligram per deciliter. Paramedics recommended hospitalization, but she declined. Later, the BHB was still elevated at 6.1 millimoles per liter.

It appears that at this point in the event, no one had stopped the study drug. She developed severe nausea, vomiting, confusion, drowsiness, obtundation, and a blood glucose of 457 milligram per deciliter.

In the hospital, labs showed a severe metabolic acidosis with a pH of 6.96 and a low bicarbonate of 4.4 milliequivalents per liter. She was treated with IV fluids, electrolytes, insulin drip, bicarb fusion, antiemetics, and antibiotics. Despite treatment, the patient died due to cardiac arrest and respiratory arrest secondary to DKA. An autopsy showed cerebral edema with herniation of cerebellar tonsils into the occipital foramen.

This case clearly was adjudicated as a certain DKA with a fatal outcome. Beyond this, it's important to consider the reliability of the DKA adjudication process. In other words, is the adjudication process in the development program reliably informing DKA risk in the real world with the use of this drug?

DKA occurs along the spectrum, and caveats to this approach of having five categories include questions about the clinical meaningfulness of the classifications as they apply to the real world. A review of the narrative of events adjudicated as unlikely ketoacidosis but ketosis showed that some

of these events were clinically significant, serious adverse events, requiring hospitalization. They also usually required an intervention to prevent further worsening of the clinical condition.

In addition, some of the criteria utilized for adjudication seemed to be designed for enhancing specificity to classify an event, which may have sacrificed sensitivity of categorizing clinically meaningful events in the certain DKA category.

For example, the requirement of two corroborating BHB values of 3.8 millimoles per liter or greater, at least 60 minutes apart but within 24 hours to classify an event as a potential DKA event. For this reason, the statistical assessment of DKA risks that will be discussed in a subsequent presentation will show not only certain DKA events but all adjudicated events.

Next, I'll review some example narratives in patients treated with empa 2.5 milligram that illustrate these points. Here's an example of a

serious adverse event adjudicated as unlikely ketoacidosis but ketosis.

A 32-year-old woman was evaluated in the emergency room for intense colicky abdominal pain, vomiting, dehydration, and ketones in the urine. The patient was hospitalized with a diagnosis of mild DKA and gastroenteritis. Treatment with infusion of insulin and intravenous fluids was initiated, and empa 2.5 milligram was temporarily discontinued.

The narrative states the next day, blood glucose was 170 milligram per deciliter and BHB was 2.8 millimoles per liter. Three hours later, a repeat BHB was 0.6 millimoles per liter and blood glucose was 60 milligram per deciliter. Later, and arterial blood gas showed a low bicarbonate of 14.3 milliequivalents per liter, a pH in the normal range, along with a low pCO2 of 20 millimeters mercury, suggesting the patient had a metabolic acidosis compensated by respiratory alkalosis to keep the pH normal. Patient was discharged two days later, and empa 2.5 milligram was restarted.

In another example, a 51-year-old woman went to the emergency room for nausea, vomiting, confusion, hyperglycemia, and an elevated BHB of 1.9 millimoles per liter and a blood glucose of 396 milligram per deciliter. She was told to replace her insulin pump and given oral hydration.

Patient's condition did not improve, and the next day, she was hospitalized for ongoing symptoms of nausea, vomiting, blood glucose of 340 milligram per deciliter, and elevated ketones, and was found to have a worsening low bicarb level of 16 milliequivalents per liter, suggesting metabolic acidosis along with a normal pH of 7.37. The maximum BHB was 4.4 millimoles per liter. Empa 2.5 milligram was temporarily discontinued, and she was treated with insulin and fluids.

The investigator documented that the patient had mild ketoacidosis, which was serious due to requiring hospitalization. We believe this event was adjudicated as unlikely ketoacidosis but ketosis at least in part because the pH was normal.

One more example is a 20-year-old woman

evaluated in the emergency room for generalized malaise, abdominal pain, vomiting, and an elevated BHB of 2.2 millimoles per liter, and a blood glucose is 164 milligram per deciliter. On examination, the patient had ketotic breath, and the abdomen was painful to palpation. An arterial blood gas showed a high anion gap of 16, a normal pH of 7.4, and a normal bicarb of 21 milliequivalents per liter. She was also diagnosed with an urinary tract infection.

The patient received treatment with fluids and insulin. Later, ketone levels returned to normal, and she was discharged from the emergency room. However, overnight she had recurrent elevated BHBs up to 2.4 millimoles per liter, which returned to normal by the next day.

The patient took the study drug. Ketone levels increased to 2.9 millimoles per liter, along with a tender abdomen and discrete tachypnea. The patient was hospitalized and serial, arterial blood gas measurements showed a normal pH of 7.36 and a worsening bicarb of 17.7 milliequivalents per

liter, suggesting metabolic acidosis; and according to the narrative, a compensatory low pCO2 of 32 millimeters mercury. Empa 2.5 milligram was permanently discontinued after which the ketone levels and symptoms improved.

The patient was hospitalized for 3 days and treated with IV fluids and insulin. The maximum BHB was 4.7 millimoles per liter. This event was considered serious due to requiring hospitalization. Note that this event was adjudicated as unlikely ketoacidosis but ketosis, but if the maximum BHB value was considered, this event would have been classified at least as potential.

The table on this slide shows total event counts for adjudicated cases. We believe looking at all three categories shown here in our analysis is the most clinically meaningful approach. To summarize, there were 3 certain, 1 potential, and 2 unlikely ketoacidosis but ketosis events in the placebo arm, and there were 2 certain, 3 potential, and 8 unlikely ketoacidosis but ketosis events in

the empa 2.5 milligram arm, for a total of 6 events in the placebo arm versus 13 events in the empa 2.5-milligram arm. Note in this tabulation, some patients could have more than one event.

In the next presentation, Dr, Gomatam will show the statistical analysis for DKA risk for the empa 2.5 milligram for all three categories using time to first event analyses.

FDA Presentation - Shanti Gomatam

DR. GOMATAM: Good morning. I'm Shanti Gomatam from the Division of Biometrics VII in the Office of Biostatistics. During my presentation today, I will focus on the statistical assessment of the risk of diabetic ketoacidosis or DKA.

No hypotheses were prespecified for the diabetic ketoacidosis endpoint in the protocol or the statistical analysis plan. There was, thus, no attempt to power the study to establish that empagliflozin 2.5 milligram dose was either noninferior or superior to the placebo arm in terms of risk of diabetic ketoacidosis.

We present descriptive analyses of the risk

of DKA using unadjusted 95 percent confidence intervals. All randomized subjects who took at least one dose of randomized treatment were included in these analyses, and DKA events that happened up to 7 days after the last treatment dose were included.

The following analyses were conducted by the FDA to assess the risk of DKA. Hazard ratios for the time to first CEC-adjudicated DKA event were estimated using a Cox proportional hazards model with fixed treatment effect for empagliflozin versus placebo.

Exposure-adjusted risk differences were computed using patient-years of exposure in the denominator instead of number of patients. For exposure-adjusted risk differences, only the first event was considered for each subject. The Newcombe hybrid score method was used to obtain 95 percent confidence intervals.

Key analyses compared the 2.5-milligram arm to the placebo arm. Supporting analyses provided comparisons of hazard ratios and exposure-adjusted

risk differences for DKA events in the EASE-2 and EASE-3 trials. Hazard ratios and exposure-adjusted risk differences for certain DKA, or potential DKA, or unlikely ketoacidosis but ketosis events, are also provided. For convenience, we may also refer to unlikely ketoacidosis but ketosis events as UKBK in the rest of our presentation.

The analyses presented in the next few slides focus on -- sorry. As Dr. Niyyati mentioned earlier, the Clinical Events Committee charter predefined the categories for CEC adjudication of DKA events. The CEC classified the DKA events sent for adjudication as certain, potential, unlikely ketoacidosis but ketosis, or unlikely ketoacidosis, or unclassifiable.

The analyses presented in the next few slides focus on CEC adjudicated certain DKA events. The EASE-3 study had 241 patients each randomized and treated in the empagliflozin 2.5-milligram arm and the placebo arm, and there were a total of 5 certain DKA events in these two arms in the EASE-3 study. Analyses that include certain potential

and UKBK events are provided later as supporting evidence.

The graph on this slide shows cumulative event probabilities that is the complement of the Kaplan-Meier survival probabilities for the EASE-3 trial. The X-axis represent days from randomization and the Y-axis represents cumulative event probability for events adjudicated as certain DKA by the Clinical Events Committee.

The curve in orange represents the placebo arm; that in green represents the empagliflozin 2.5-milligram arm, the only dose under consideration for the type 1 diabetes mellitus claim. The curve in blue represents the 10-milligram arm, and the one in purple represents the 25-milligram arm. The cumulative event probabilities for the empagliflozin 10-milligram and 25-milligram arms are numerically higher than that for the 2.5-milligram arm.

We have here estimates of the hazard ratios and exposure-adjusted risk differences for the occurrence of CEC adjudicated certain DKA in EASE-3

for the 2.5-milligram dose of empagliflozin. As mentioned earlier, the trial was not powered for the DKA endpoint. Only 241 patients each were randomized and treated in the 2.5-milligram dose arm and the placebo arm in the EASE-3 trial.

Although the estimate of the hazard ratio for the empagliflozin 2.5-milligram arm versus placebo was 0.66, since there were only 5 events between the empagliflozin 2.5 arm and the placebo arm, the upper bound of the 95 percent confidence interval is 3.92. Therefore, an increased risk of almost 4 times as much as that in the placebo arm cannot be ruled out.

The estimated exposure-adjusted risk difference of negative 0.89 had an associated 95 percent confidence interval of negative 5.71 to 3.60. Also included here are the estimates for the incidence of certain DKA in the 10-milligram and 25-milligram doses of the EASE-3 trial, which were the only doses studied in the EASE -- sorry -- of the EASE-2 trial, which were the only doses studied in the EASE-2 trial. I'm sorry. That's a mistake.

Also included here are the estimates for the incidence of certain DKA in the 10-milligram and 25-milligram doses of the EASE-3 trial, and these were the only doses studied in the EASE-2 trial. Hazard ratios of 1.93 and 1.98 for these doses are numerically above 1, but the associated nominal 95 percent confidence intervals include the null value of 1. Exposure-adjusted risk difference estimates show similar patterns. Although point estimates are higher than zero, the associated confidence intervals include zero.

There was only one trial, EASE-3, which studied the 2.5-milligram dose for which the type 1 diabetes mellitus indication is being sought. One concern is whether the results for the DKA risk from this trial are consistent with the results for the DKA risk from the other phase 3 trial, EASE-2.

The graphs in the plot on this slide compare the probabilities of cumulative incidence of certain DKA in the EASE-2 and EASE-3 trials. Along the X-axis, we have days from randomization and the Y-axis represents a cumulative event probability.

The 52-week EASE-2 trial is on the left, while the 26-week EASE-3 trial is on the right. The orange curves represent placebo; the green curve represents the empa 2.5-milligram dose. The blue represents the empa 10-milligram dose, and the purple represents the empa 25-milligram dose. Recall that the EASE-2 trial did not include the 2.5-milligram dose.

A dashed red line is drawn at day 190, the day after the 26-week plus 7-day follow-up for DKA in the EASE-3 trial ended. The placebo curves look similar in both trials. The empa 25-milligram arm also looks similar across the two trials up to 26 weeks, but the incidence curve for the 10-milligram dose in the EASE-2 trial is visibly different from that in the EASE-3 trial.

This table compares the hazard ratio and exposure-adjusted risk difference estimates for the 52-week EASE-2 trial on the left and for the 26-week EASE-3 trial on the right. The hazard ratio and exposure-adjusted risk differences, highlighted in green, are those for the

2.5-milligram empagliflozin dose in EASE-3.

We see differences in the results for the 10-milligram dose across the two trials. The 10-milligram arm in the EASE-2 trial had a hazard ratio estimate of 4.87 with a 95 percent confidence interval for the hazard ratio that went from 1.41 to 16.83.

In the EASE-3 trial, the hazard ratio estimate for the 10-milligram dose was 1.93 with a 95 percent confidence interval from 0.48 to 7.72. The 95 percent confidence interval for the exposure-adjusted risk difference for the 10-milligram dose in the EASE-2 trial excluded and was above zero, while that for the 10-milligram dose in the EASE-3 trial included zero.

A review of baseline demographic and clinical characteristics for the EASE-3 and EASE-2 trials did not provide potential explanations for apparent differences in the 10-milligram group across the two trials; neither did a review of the pharmacokinetic exposures. Trial conduct also appeared similar across the two trials as did DKA

prevention strategies.

As Dr. Niyyati discussed earlier, due to concerns that the events in the potential and unlikely ketoacidosis but ketosis categories were clinically meaningful events, we performed analyses of events adjudicated as certain DKA, potential DKA, or unlikely ketoacidosis but ketosis. These results are presented in the next few slides.

Cumulative event probabilities for certain DKA, potential DKA, or UKBK events are plotted on this slide. The X-axis represents days from randomization and the Y-axis represents the cumulative event probability. The table at the bottom gives the number at risk for each of the 4 arms in the EASE-3 trial. The estimated cumulative event probability for the empa 2.5-milligram dose is now numerically higher than that for the placebo arm.

As seen for certain DKA, the 25-milligram empa dose in the purple curve is numerically higher than the cumulative event probability for the 10-milligram dose in the blue curve, which is

numerically higher than the cumulative event probability for the 2.5-milligram dose.

For CEC-adjudicated certain DKA, potential DKA, or UKBK events, estimated hazard ratio versus placebo for the 2.5-milligram arm was 1.5 with an associated confidence interval with an upper bound of 4.20. These estimates were based on a total of 15 events across the empa 2.5-milligram arm and the placebo arm in the 26-week long EASE-3 trial.

An exposure-adjusted risk difference of 2.49 was estimated for the 2.5-milligram dose versus placebo with an associated 95 percent confidence interval that included the null value of zero.

I'm sorry; my animations have a mind of their own. For the 10-milligram and 25-milligram doses, the estimated hazard ratios were 3.96 and 4.65, respectively -- sorry, I'm still here -- with associated 95 percent confidence intervals that excluded and were above the null value of 1. Similarly, exposure-adjusted risk differences for the two higher doses were estimated to be greater than zero with associated 95 percent confidence

intervals that excluded and were above the null value of zero.

In summary, hazard ratios and exposure-adjusted risk differences for all three doses versus placebo are greater than the null value of 1 and 0, respectively. The associated 95 percent confidence intervals for the 2.5 dose include the null value, while those for the 10-milligram and 25-milligram doses do not.

Cumulative event probabilities are compared here for the EASE-2 and EASE-3 trials. Along the X-axis, we have days from randomization and the Y-axis represents the cumulative event probability. The 52-week EASE-2 trial is on the left, while the 26-week EASE-3 trial is on the right.

The orange curve represents placebo; the green curve represents empa 2.5-milligram dose. The blue represents the empa 10-milligram dose, and the purple represents the empa 25-milligram dose. Recall that the EASE-2 trial did not include the 2.5-milligram dose.

As before, the dashed red line is drawn at

day 190, the day after the 26-week plus 7-day follow-up for the EASE-3 trial ended. As mentioned earlier, we did not find obvious differences in baseline demographic or clinical characteristics, pharmacokinetic exposure, trial conduct, or DKA prevention strategies that could explain the apparent numerical differences in the estimates across trials.

Hazard ratio estimates for all doses are greater than 1 in both trials. To recap, a hazard ratio estimate of 1.5 was obtained for the empa 2.5 dose with associated 95 percent confidence intervals from 0.53 to 4.2. The 95 percent confidence interval for the exposure-adjusted risk difference for the 2.5-milligram dose arm was greater than zero, but the associated CI included zero. Ninety-five percent confidence intervals for risk difference estimates for the two higher doses in both trials exclude and are above zero.

Sorry. I should also have mentioned that for the two higher empa doses, the 95 percent confidence intervals for the hazard ratio in both

trials exclude and are above the null value of 1.

There are limited data available for the assessment of DKA risks for the 2.5-milligram arm. A total of 482 patients were randomized and took at least 1 dose across the empa 2.5-milligram and placebo arms. Five patients in total across the 2.5-milligram and placebo arms had a certain DKA event. The hazard ratio estimated for certain DKA was less than one with a CI that covered 1.

A negative exposure-adjusted risk difference was estimated for certain DKA with an associated confidence interval that included zero. Fifteen patients in the 2.5-milligram arm and the placebo arm had either certain DKA, potential DKA, or unlikely ketoacidosis but ketosis events.

The hazard ratio estimated here for the 2.5-milligram arm of EASE-3 versus placebo was 1.5. The 95 percent confidence interval had a lower bound of 0.53 and an upper bound of 4.20. The upper bound estimated for the exposure-adjusted risk difference confidence interval was 9.28.

The results from EASE-3 did not appear

consistent with those from EASE-2, raising concerns about potential generalizability of the results from EASE-3. No differences that could potentially explain inconsistencies were noted in baseline demographic or clinical characteristics, pharmacokinetic exposures, trial conduct, or prevention strategies for DKA.

Subgroup analyses were not possible for the 2.5-milligram dose alone in the EASE-3 trial, however, we did conduct subgroup analyses with all doses combined for certain DKA in EASE-3, and noted no subgroup interactions.

Dr. Niyyati will now summarize and present concluding remarks.

FDA Presentation - Mahtab Niyyati

DR. NIYYATI: I'm now going to summarize the safety and efficacy of the empa 2.5-milligram dose and provide our benefit-risk assessment. In EASE-3 at week 26, a statistically significant, placebo-adjusted reduction in HbA1c of 0.26 percent from baseline was observed in patients treated with empa 2.5 milligram. The change in HbA1c the

placebo group was an increase of 0.2, and the change in HbA1c in the empa 2.5 milligram was a decrease of 0.05 percent. Data suggests no difference from placebo with regard to hypoglycemia risk.

In addition, a continuous glucose monitoring substudy, which included a relatively small number of patients, examined blood glucose profiles. The small sample size limits interpretation, but the findings suggested a small reduction in time spent in hyperglycemia and no impact on time spent in hypoglycemia.

Empa 2.5 milligram showed the reduction of 1.77 kilograms in body weight when compared to placebo. Note the baseline mean BMI for the empa 2.5-milligram dose was 28 kilogram per meter squared and the baseline mean weight was 81.4 kilograms. Empa 2.5 milligram showed the reduction of 2.01 millimeters mercury in systolic blood pressure compared to placebo. The mean baseline systolic blood pressure for empa 2.5 milligram was 123.5 millimeters mercury.

A reduction of 0.35 millimeters mercury in diastolic blood pressure for empa 2.5 milligram dose compared to placebo was also observed. The mean baseline diastolic blood pressure was 75.2 millimeters mercury.

Putting this all together in a benefit-risk framework, when considering efficacy findings for empa 2.5-milligram group, we have a small reduction in HbA1c, a surrogate endpoint for microvascular outcomes. Indeed, the magnitude is within the noninferiority margin that we often use in comparative effectiveness studies for diabetes drugs.

The magnitudes of change for the other clinical benefits, including blood pressure and body weight, is also quite small and of uncertain clinical relevance, especially in patients who are normal weight or normotensive at baseline. When considering the risk of DKA for empa 2.5 milligram, there's insufficient information to be reassured about the risk of DKA.

The size of the database submitted to

support safety of the 2.5-milligram dose is relatively small and of short duration. Only 241 patients were randomized to the 2.5-milligram dose in a single phase 3 trial. When looking at only the certain DKA category, the small number of DKA events limits the ability to discern meaningful differences between groups.

In addition, it's unclear whether categorization made clinical sense, as some of the DKA events adjudicated as unlikely ketoacidosis but ketosis were clinically meaningful. In addition, the intense monitoring and clinical support in the clinical trials raises questions about the generalizability of these findings to the real world, where less rigorous implementation of monitoring may result in more frequent and more severe DKA events.

Lastly, further differences in DKA risk between the two phase 3 trials conducted in the type 1 population were observed for the empa 10-milligram dose, which could not be explained, highlighting that with a small safety database,

results can be variable across trials, raising concerns about the generalized ability of the finding.

As an exploratory benefit-risk assessment, we considered the 6-month time horizon, the EASE-3 trial duration, as well as a 6 and a half year time horizon to leverage outcomes data from the DCCT. For benefit, we estimated a 12.8 percent reduction in microvascular complications associated with glycemic control achieved in DCCT out to 6.5 years of trial intervention.

Clinically, the microvascular complications prevented could have very different severities, from a reduced risk of microalbuminuria, mild vision problems or nerve pain, to reduced risk of end-stage renal disease, blindness, or amputation. The absolute risk reduction will vary based on the baseline risk of each microvascular complication.

There's a potential, but as yet, undemonstrated reduction in the risk of microvascular complications resulting from the reduction in HbA1c associated with empa 2.5

milligram. The quantification of estimates of this benefit is difficult because the estimates assume that patients are able to maintain the 0.26 percent HbA1c reduction beyond 6 months; but we note that in EASE-2, that studied the higher doses over 52 weeks, the HbA1c reduction at 52 weeks was roughly 10 to 30 percent less compared to week 26, based on the sponsor's results.

Given these uncertainties, the true benefit to patients treated with empa 2.5 milligram may be smaller.

For DKA risk at 6 months, we considered DKA risk estimates based on the phase 3 trial. Based on the exposure-adjusted risk difference estimate for certain, potential, and unlikely ketoacidosis but ketosis events, we estimate there would be 125 additional patients with events or up to 468 additional patients with events per 10,000 patients treated.

As for DKA risk at 6 and a half years follow-up, without long-term data, we must estimate risk based on the observed data from the 6-month

trial. We estimate that treating 10,000 patients for 6 and a half years could result in 1,494 additional patients with events of certain, potential, or unlikely ketoacidosis but ketosis if risk is constant over time.

We recognize that our estimates are uncertain and subject to certain assumptions. For benefit, we assume that the quantitative association between HbA1c reduction and microvascular risk reduction observed in DCCT applies in light of evolving clinical practice, such as therapies to control risk factors from microvascular disease, such as ACE inhibitor and ARB therapy.

As for the risk of DKA, limited data is a source of significant statistical uncertainty, but it's clinically unlikely that empa reduces the risk of DKA. The possible likely higher risk of DKA in the real world, compared to the clinical trial setting, means estimates provided here, including their statistical bounds, likely underestimate the true risk of DKA.

This concludes the FDA presentations. We look forward to hearing the committee's discussion and recommendations on this application. Thank you in advance for participating in this meeting and helping FDA fulfill its mission of protecting and promoting public health by helping ensure human drugs are safe and effective for their intended use.

Clarifying Questions to FDA

DR. BURMAN: Thank you very much.

We will now proceed to clarifying questions for the FDA. We have about 15 or 20 minutes for those. Dr. Nason is first.

DR. NASON: Okay. I hope you'll actually permit me two quick questions; I think they're both quick. The first one was on slide, I guess, 13. On the statistical assessment of DKA risk, you're using 9 out of 241, I believe, events in the empa 2.5-milligram dose group to come up with a hazard ratio of 1.5. But the presentation just before you with Dr. Niyyati had had a 13 there, and I just wanted to clarify whether it was 13 events among

9 patients.

Is that the discrepancy?

DR. GOMATAM: Yes, that is correct, 13 events and 9 patients.

DR. NASON: Okay. Because this is a little misleading because it says events in the heading of this table --

DR. GOMATAM: Oh.

DR. NASON: -- so that would be good to clarify.

DR. GOMATAM: Thank you. I apologize for that.

DR. NASON: No, that's fine. That's just why I wanted to clarify. So there were 4 patients or maybe less that had multiple events.

DR. GOMATAM: Right. On the analysis page, we did clarify that we were only analyzing the first events in patients.

DR. NASON: I see.

DR. CHRISCHILLES: But, yes, I agree that it can be confusing if you just look at the table.

DR. NASON: Okay. Then my second question,

which again I think is just clarification, this is for Dr. Crackel. On the primary endpoint, you'd made a comment that the 95 percent confidence interval for the HbA1c did not include zero, and therefore that was statistically significant. But as I understood it, the alpha spending rule for the protocol would have only had about alpha 0.01 by the time you got to judgment of statistical significance.

So I was just trying to figure out if that was an adjusted confidence interval, because I would think a 99 percent confidence interval would be used to judge significance there.

DR. CRACKEL: The confidence interval [inaudible - off mic].

DR. NASON: Sorry. This was slide 8 of Dr. Crackel's presentation.

DR. CRACKEL: The confidence interval reported is a 95 percent confidence interval.

DR. NASON: So to be consistent with the protocols alpha spending, it would have been a 99 percent confidence interval, I think; at least

that's how I would -- since it's 0.01 allocated to that comparison?

DR. CRACKEL: I'd have to double check that.

DR. NASON: Okay. Thank you.

DR. BURMAN: Thank you. Just a reminder to state your name and who you are specifically addressing for the question.

Thank you. Dr. Munir?

DR. MUNIR: Kashif Munir. I guess the crux of the matter really is DKA risk. You had shown three representative examples of this UKBK classification in patients that clearly had symptoms, so they shouldn't be classified that way.

I guess the question is there were 8 UKBK patients in the 2.5-milligram group; what about the other 5 patients, or since there's such a low number, should we reclassify all of these and really do a proper analysis of which patients were really at higher risk versus not? Because that's really going to come down to, I think, a major part of how people go with this and the safety that's really expected from this dose.

DR. NIYYATI: To answer the first part of your question, there are additional patients that may belong to the higher risk category, based on the case definitions provided in the adjudication charter.

Do you want to comment further?

DR. YANOFF: So we did consider re-adjudicating, but didn't feel that was a really fair way to do the analysis, given that we had already seen the unblinded data. So our next best approach was to look at all the categories together, recognizing there is uncertainty there.

So if you feel that there's some uncertainty in the way the adjudication was done, we would like to hear what you would prefer and if you think any additional data are needed to help clarify the risk.

DR. MUNIR: I don't know if there's uncertainty. I guess the whole question is that, these three cases, there were definitely symptoms. So it looks like, by definition, you can't be UKBK if that's the case.

DR. YANOFF: We went back and forth between are these misadjudicated, not following the rules, or is something about the adjudication category or process causing this to happen. It was difficult to figure that out because of how complicated the adjudication categories were.

We have that in a backup slide if it would be helpful for you to see exactly how complicated it was and how many different doors you could go through once you found one lab value or symptom where you were supposed to go next. And ultimately, where the patient ended up was just super complicated. This is I think the most fair way to relook at it.

DR. BURMAN: Do you want to show that slide?

DR. NIYYATI: I would also like to clarify a point that the applicant made about certain DKA that would have been acidosis plus ketosis. If you look carefully at the potential DKA category, they also have an acidosis plus ketosis category as classified as potential. I just wanted to clarify that, that, dependent on the level of bicarb, if

it's less than 15, it would fall into certain, but if it's less than 18, it would fall into potential.

DR. BURMAN: Thank you. This slide is complicated.

(Laughter.)

DR. BURMAN: Do you want to summarize it a minute?

DR. NIYYATI: I'll try. So as the applicant mentioned, if there is an established acidosis, pH of less than 7.34, or a bicarb of less than 15, that would fall into a certain DKA category. The potential category is a wide spectrum from elevated BHBs with various cutoffs, along with symptoms, all the way to acidosis plus ketosis, or just acidosis, or just ketosis.

The unlikely ketoacidosis but ketosis group are any blood BHB that would fall between 1.5 to 3.8 and one of the below criteria. Either the pH has to be normal or the patient has to be asymptomatic. It's a little complicated.

DR. BURMAN: I think we'll be glad to look at that further, later. Thank you.

Dr. Wang?

DR. LOW WANG: Cecilia Low Wang. Actually, just following up on that, I have a couple of questions. This is going back to slide 11 of Dr. Niyyati's. Of those 8 cases in the empa group that were unlikely ketoacidosis but ketosis, there were the three that looked like those were SAEs. So which of the other five were SAEs?

DR. NIYYATI: The other five were not SAEs. They're an additional, at least 2 patients, adjudicated as unlikely ketoacidosis but ketosis, that according to the case definition will fall into potential. For example, there is one patient with a BHB of 6 millimoles per liter, which is pretty high, in addition to a bicarb of 18. By definition, that falls into potential, and that has been adjudicated as unlikely ketoacidosis but ketosis.

In order to find out about further information about this particular patient, we had to look at narratives in other places such as the CSR. That information was not provided in the

adjudication package in order to put it together. The other patient was a recurrent BHB elevation of 3.8 millimoles per liter, which is one of their definitions for potential DKA; that if you have recurrent BHB elevations, that would fall into potential, and this particular patient had recurrent BHBs more than 3.8.

DR. LOW WANG: So in addition to the three that were outlined, there were two additional ones. Okay.

Then the other question I have is related to Dr. Crackel's presentation. I was wondering what the FDA thought about the Diabetes Treatment Satisfaction Questionnaire results. There was no comment about that.

DR. YANOFF: I'd like to invite to the microphone
a member of our clinical outcome assessment staff.

DR. DASHIELL-AJE: Hi. This is Ebony Dashiell-Aje. We recognize the results that you presented in slide CC-50, and while the application is still under review at FDA, we are concerned that

the Diabetes Treatment Satisfaction Status Questionnaire is not fit for purpose to assess improvement in treatment satisfaction in the proposed context of evaluating the efficacy of empagliflozin.

DR. BURMAN: Thank you. Dr. Blaha?

DR. BLAHA: Mike Blaha. A follow-up question, I guess, to any of the FDA staff that really is similar to Dr. Low Wang's question. The two incremental potential cases in the 6 potential, incremental, unlikely ketoacidosis but ketosis cases -- and I think the question was sort of asked in a different way, and I'm trying to get at the clinical significance -- do we have the numbers on how many of those were hospitalizations, for example?

DR. NIYYATI: Three of them are hospitalized, and those are the ones that were presented --

DR. BLAHA: In phase [inaudible - off mic].

DR. NIYYATI: Yes.

DR. BURMAN: Thank you. Dr. Brittain?

DR. BRITTAIN: I guess my question, you could look at slide 16 of the statistical assessment of DKA risk. I did want to say the FDA presentation was also great.

I'm interested in whether there's any way of finding risk factors for the DKA. In that slide, that slide 16, there's a bullet point that says, "No subgroup interactions noted for certain DKA." A test of interaction tends to have very low power, so it could be hard to detect an interaction that is real, plus you use certain rather than the bigger three-level category of DKA we'd been talking about.

So I'm wondering did you look at that, the broader categories, and also was there anything that looks suggestive
at all?

DR. GOMATAM: Shanti Gomatam, FDA. Yes, I agree, and with only 5 events, there wasn't much hope of seeing anything in the certain DKA. I did look at all three categories together. I wasn't done in time to get it on to the slides. The only

thing I saw there was when I combined all doses, sex, protective in males and harmful in females. That was the only interaction I saw; no others.

DR. BRITTAIN: I have a little bit of a follow-up to this. One of the things I'm wondering about -- and this is more a clinical question -- is the patients who have the biggest drop in their hemoglobin A1c, are they possibly at higher risk for DKA? That's not a baseline characteristic, but I'm wondering about that tension between efficacy and safety that we've heard about.

DR. YANOFF: While this program is limited, there is literature on this issue, in general, that there are risk factors for DKA, but they don't seem to be -- there doesn't seem to be any interaction with the SGLT2 treatment. So higher A1c, pump use, and female gender are risk factors, but they don't seem to be affected by treatment with the SGLT2.

DR. BURMAN: Thank you.

DR. YANOFF: We have one FDA comment also to address Dr. Nason's previous question.

DR. BURMAN: Sure.

DR. WANG: Hi. This is Yun Wang, statistical team leader supporting antidiabetic product development. For Dr. Nason's question for Dr. Crackel's slide 8, about 95 percent confidence interval for the change in HbA1c, yes, based on the testing hierarchy, it only assigned 0.01 alpha to testing HbA1c change.

If we stick with that, that would be 99 percent confidence interval. We did calculate that. The 99 percent confidence interval for the difference in change in HbA1c will be minus 0.44 to minus 0.07. So the 99 percent confidence interval still excludes zero. It's still statistically significant. We present the 95 percent confidence interval for common sense. Thank you.

DR. BURMAN: Thank you very much.

We have 4 minutes before break for lunch and we have 9 or 10 questions. We will ask you to be brief and state your name. We'll probably get through one or two more questions before lunch, and then try to catch up, if we can, later.

Dr. de Lemos?

(Dr. de Lemos gestures no.)

DR. BURMAN: Okay. Dr. Everett?

DR. EVERETT: Just a quick question to follow up on Dr. Nason's question about slide 11. Have you calculated, in sort of a total events analysis, a rate ratio or looked at the incidence rate for this global DKA event, rather than a first event analysis? Do you have a number or rate ratio that we can --

Do you understand my question?

DR. GOMATAM: Could you please repeat it?

DR. EVERETT: You did a great job presenting the time to first event. I'm interested in the overall risk in a more of a total events analysis, with the perspective of how much risk and what the incidence rate is in each treatment group, and then what a rate ratio might be with a negative binomial model approach.

DR. GOMATAM: Sure. We did look at rate ratios. I personally didn't look at recurrent events, but one of our data analysis teams did, and the results look very similar. They're

qualitatively pretty much the same as I obtained with my analysis.

For certain DKAs, obviously, for the 2.5 and placebo, there were no repeat events, so 5 events and 5 patients. For the certain, potential, and UKBK, there were 13 events and 9 patients, but the results looked very similar as far as I could see using recurrent event analysis. I did not do risk ratios on that case.

Did that answer your question?

DR. EVERETT: Thank you.

DR. BURMAN: Thank you. Last question before lunch, Dr. Newman?

DR. NEWMAN: I have a question about DKA identification. Did you say that there were possible cases of DKA that were not identified and not sent to adjudication? And if so, do you have an estimate, too?

DR. YANOFF: No. Dr. Niyyati outlined BHB levels that were not sent, and I'll let her clarify that.

DR. NIYYATI: That was according to the

charter. The charter specified that ketone levels between 1.5 and 3.8, without symptoms, are not to be sent to adjudication.

DR. NEWMAN: Oh. Thank you.

DR. BURMAN: Thank you for keeping that short. Dr. Weber, the last question, please.

DR. WEBER: Sure. This is Tom Weber. This is for Dr. Penzenstadler. The slide 7 worst-case analysis, I was interested in that. I am to conclude from this -- this is the worst-case analysis, so the average run on the simulations is substantially higher in terms of the estimated difference in A1c versus placebo?

DR. PENZENSTADLER: Yes.

DR. WEBER: Okay.

(Laughter.)

DR. BURMAN: Even though it's lunchtime, could you expand for just a minute?

(Laughter.)

DR. PENZENSTADLER: You said keep it short. We did the 95 percent confidence interval in this worst-case scenario because there's a lot of

uncertainties with the modeling approach. People aren't very comfortable with it. I do have an estimand for what the model would predict on a median level. I don't have that estimand ready right now, but I can have that after lunch. Thanks.

DR. BURMAN: That would be great, and thank you for keeping it short.

We will now break for lunch. We will reconvene again in this room in one hour from now at 1:00. Please take any personal belongings with you. Committee members, please remember there may be no discussion of the meeting during lunch amongst yourself, with the press, or with any other member of the audience. Thank you.

(Whereupon, at 12:00 p.m., a lunch recess was taken.)

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

(12:59 p.m.)

Open Public Hearing

DR. BURMAN: Good afternoon. We will be starting the afternoon 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 it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the subcommittee of any financial relationships you may have with the sponsor, its product, and if known, indirect competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance.

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

Will speaker number 1 please step up to the podium and introduce yourself. Please state your name and organization you are representing for the

record. Thank you.

DR. KURIAN: Good afternoon. My name is Martin Kurian, and I'm here to speak on behalf of Dr. --

DR. BURMAN: Could you be a little closer to the microphone?

MR. KURIAN: My name is Martin Kurian, and I'm here to speak on behalf of Dr. Charlie Alexander.

"Dr. Alexander is an endocrinologist with more than 35 years of experience in diabetes. Since 2016, he has worked part time for Kinexum and others providing consulting services to pharmaceutical and medical device companies. He had worked at Merck for many years and retired in 2015. Prior to Merck, he treated many patients with diabetes. He has no relevant disclosures

"After the discovery of insulin treatment, which prevented immediate death from diabetic ketoacidosis, cardiovascular and renal complications of diabetes have become an increasingly serious problem for people with

diabetes.

As this study shows, the female advantage with women having less coronary heart disease than men disappears with diabetes. Unfortunately, insulin does not prevent either cardiovascular or renal complications, and there has been a long-term need for more effective treatments for both of these complications.

SGLT2 inhibitors have repeatedly shown their ability to improve both cardiovascular and renal outcomes in large clinical trials enrolling study participants with type 2 diabetes. This slide shows results from the EMPA-REG study with fear of the primary endpoint of cardiovascular events with empagliflozin treatment.

Importantly, the cardiovascular and renal benefits do not correlate at all with glycemic efficacy. For example, patients with renal impairment have little glucose lowering from SGLT2 inhibitors but saw substantial improvement in renal outcomes in the CREDENCE study.

"Indeed, SGLT2 inhibitors are a proven oral

therapy, however, patients with type 1 diabetes, the risk of DKA is the major limiting factor. With this slide showing data for sotagliflozin, DKA is not just an inconvenience for those living with type 1 diabetes. It can be lethal, as seen in the empagliflozin clinical development program for type 1. An important complicating factor is that DKA in this situation can have near normal blood glucose levels or only mild hyperglycemia, which can delay recognition and treatment.

"An SGLT2 inhibitor, which does not increase the risk of DKA compared to placebo, would be very helpful and would markedly improved the benefit-to-risk ratio of the medicine. Reduction of glucose-lowering efficacy when people with type 1 diabetes are treated with SGLT2 inhibitors may not be at all relevant for their ability to improve cardiovascular and renal outcomes.

It is not known if the CV and renal benefits correlate with the dose of SGLT2 inhibitor. It is possible that much lower doses will continue to provide these important benefits.

"Dr. Alexander expects that there will be continued off-label use of SGLT2 inhibitors among patients with type 1 diabetes, eager to benefit from the improved cardiovascular and renal outcomes observed in studies of type 2 patients. FDA approval of an SGLT2 inhibitor for type 1 diabetes may increase the number of patients with diabetes able to benefit from this class of medicines. Thank you."

DR. BURMAN: Thank you very much. Will speaker number 2 step up to the podium and introduce yourself? Please note your name and any organization you are representing.

MS. CLOSE: Good afternoon. My name is Kelly close. I'm a cofounder of the diaTribe Foundation, Close Concerns, dQ&A. dQ&A is a diabetes market research organization that has a panel of 18,000 patients throughout the United States, Canada, and multiple countries in Europe, and I'm going to be sharing some data today that reflects opinions of the thousands of type 1 patients about their diabetes care, broadly

speaking, and specifically about some of their views on SGLT2 inhibitors.

The data isn't meant to be generalizable, but it's illustrative of some people taking SGLT2s that aren't currently regulated. By way of disclosure, the sponsor, as well as dozens of other for-profit and nonprofit organizations, work with dQ&A, Close Concerns, and diaTribe.

diaTribe is a 501(c)(3) nonprofit. It's funded by the Helmsley Charitable Trust, the Ella Fitzgerald Foundation, as well as a number of manufacturers, and families, and individuals. I don't have any relevant personal disclosures, except that I've had type 1 diabetes for 35 years.

Hold on one quick second. I just received a really meaningful quote from someone who couldn't be here today, Dr. Jen Scherer of Yale. A lot of what we care about -- she also has diabetes -- is the barriers that people with diabetes face, and I just wanted to read this to you quickly.

"Diabetes is a daily battle of minimizing highs and lows, avoiding and avoiding hypoglycemia.

It's imperative to find new ways to help patients achieve success. So how can we safely employee agents that may increase the risk of DKA? Education. We must replace our glucose-centric approach to ketone assessment with new and existing tools to guide placement and provider use of SGLT2s."

The renowned John Buse of University of North Carolina said that he believes that there's a 95 percent chance that SGLT2 inhibitor use in people with type 1 diabetes with chronic kidney disease or heart failure would reduce heart failure hospitalizations and chronic kidney disease progression in patients; and he and other [inaudible - mic fades] would like to see this studied. People with type 1 diabetes would also.

So I just want you guys to remember the chance that you have to public health, by thinking very creatively about a conservative approval of this drug is a big deal.

We all know, obviously that there is a massive unmet need with people with type 1

diabetes. And I'm not going to go through this in depth, but to say I'm in that last group, the over 50 group. The fact that over 70 percent of us are not at our A1c targets, given all of the good that FDA has done, is tragic, and this we know can change over time, and we hope that it will.

We also wanted to just go through a little bit of the barriers that people have in addressing type 1 diabetes. You can see that high and low blood sugar come into the conversation really quickly. We just want to be normal. We just want to be normal. Okay? People with type 1 have gone on to SGLT2s for multiple reasons. According to the 90 people with whom dQ&A has communicated, what's driving off-label use, you can see there it's lower A1c. People want to have fewer highs and lows. They want to have more normal lives.

FDA, of course, obviously doesn't practice medicine, but it can really help with advice on patient selection, and I would love for you to keep that in mind. FDA has done so much good on risk stratification, and we would love for you to

consider guiding doctors on the types of patients who would benefit and what risk mitigation bucket to put them in; and which patients should be discouraged from taking SGLT2 inhibitors. That's possible, and that will happen with a conservative approval.

Otherwise, particularly doctors, who have little time with patients, might just prescribe off label without education, and then inadvertently a decision against approval by you has a chance of prompting broader use without education, and we all know that sends chills up and down our backs. That's an unintended consequence that we really want to avoid.

That's what happens with popular unregulated drugs that payers cover, and we know, by the way, that many, many payers are covering this drug for people with type 1 because of the impact on blood glucose, mainly and particularly reduction of hypoglycemia.

This is really scary. These are 90 people who are taking this drug, and most of them actually

haven't been trained, and you would think that they would have been. This can change, and this can be the result of something that you do. If you want to know if patients will spend time on this, they will. Also, if patients don't want to spend time on training, you can tell them that they can't have it, and the medical community will follow what you say.

I'm going to go through the end of this just very quickly to say that it's a new day in type 2. All of us in type 1 are watching what's happening in type 1. They're not just taking medicine to reduce glycemic benefits. They're also taking it to improve their cardiovascular risk and kidney risk, and this is an amazing impact that FDA has had on public health.

I would just love for you to spend some time thinking about the impact that FDA has had and thanking yourselves, because you made some pretty big decisions in what you are prompting with so many sponsors in the last days. Those are some pieces that will be on diaTribe.org tonight.

There are some ideas from patients. We want to work with you as stakeholders to keep patients as safe and healthy as possible. This is a piece that we worked on with JDRF with Beyond Type 2, with ADA, with ACE, with ENDO, and with AADE. We can work together as stakeholders. This has made many people who have had DKA from pump use, not SGLT2 use, even smarter about how to address it.

The last thing is if you think that time and range, it might not be fully validated, the work that Roy Beck and Rich Bergenstal has shown in starting to validate it, you guys are the ones who made time in range through this bold, bold work that you did in 2017. Every time my time in range move 5 percent, you might think that 6 percent you saw on those slides is not a big deal. It is a big deal. It's 10 hours a week that I'm more in range.

Thank you very, very much for your attention and for all the incredible work that we have from FDA as patients.

DR. BURMAN: Thank you very, very much. Will the next speaker step up to the podium and

introduce yourself? Please state your name and any organization you're representing.

DR. DUTTA: Good afternoon. My name is Dr. Sanjoy Dutta. I'm the vice president of research with JDRF International, the leading charitable organization funding type 1 diabetes, or T1D research, with a mission to accelerate life-changing breakthroughs, to offer better treatments along the way to curing and eventually preventing T1D. JDRF does not have any financial disclosures.

The key points I'll focus on today are, 1) the unmet need in T1D; 2) the benefits of SGLT2 inhibitors, including the clinical meaningfulness of the HbA1c C reduction, as well as outcomes beyond A1c; and 3) the risks of SGLT2 inhibitors and appropriate risk management. The mainstay of T1D disease management, insulin, has been around for almost a hundred years now, but it is not a cure. Significant unmet needs and disease management burdens still exist, particularly considering the lower age of onset and longer

disease duration in people with T1D.

Today, people with T1D and their caregivers are responsible 24 hours a day and often minute-to-minute disease management needed to survive. While technology to administer insulin and monitor glucose levels have improved, subcutaneous, exogenous insulin replacement does not work the same as endogenous insulin in those without diabetes, leading to significant challenges with glucose control and subsequent risks of increased complications.

Data published earlier this year from the T1D Exchange clinic Registry tells us that less than a third of the adults and a fifth of the children in the U.S. meet recommended glycemic targets as measured by hemoglobin AS1c. The average patient spends 7 hours a day hyperglycemic and over 90 minutes a day hypoglycemic. Because of the state of diabetes care, there is a need for innovative, safe, and effective therapies for people with T1D, in addition to insulin that improve glycemic control and both short- and

long-term outcomes.

As we have heard today, data from the phase 3 EASE program shows that empagliflozin improved hemoglobin A1c statistically significantly, and there was no increase in hypoglycemia below 54 mg per deciliter. There is published consensus among the diabetes community of clinicians, patients, researchers, and foundations and funders that hemoglobin A1c, as well as hypoglycemia, hyperglycemia, time in range, and diabetic ketoacidosis are all clinically meaningful outcomes for T1D.

While these outcomes may be seen as short-term benefits, patients' repeated exposure to these outcomes over time contribute to the long-term consequences of T1D. These outcomes are not insignificant and are clinically meaningful. Therapies that offer improvement in these outcomes, even if small, and balanced against appropriate risk can help address some of the unmet needs in this disease.

Turning to the risks, as we have heard, a

known safety concern with the use of SGLT2 inhibitors is the increased risk of diabetic ketoacidosis. Considering that this drug class has important benefits for people with T1D, a risk evaluation and mitigation strategy, or REMS, would be an appropriate mechanism to manage the known risks.

We believe a REMS is appropriate since its purpose is to focus on preventing, monitoring, and managing a specific serious risk, such as DKA in this case, by informing, educating, and reinforcing actions to reduce the frequency and severity of the event.

Importantly, the clinical community of experts have carefully considered this risk, and international consensus on the safe management of DKA risk in T1D patients taking SGLT2 inhibitors has been established. The consensus has been published in diabetes care, a recognition of the importance of information for the safe use of this class of drugs in patients with T1D.

JDRF is committed to an offers our support

in working with the community to provide this information and education around the safe use of SGLT2 inhibitors in people with T1D. We are pleased that empagliflozin may represent an option as an adjunct to insulin for people with T1D to address the unmet need in this disease by improving glucose control and potentially reducing the risk of complications.

If determined by FDA to be safe and effective, and with appropriate risk management, therapies from this drug class as an adjunct to insulin therapy will positively impact the lives of people with T1D.

We thank the committee, FDA, and the sponsor for the careful consideration of the benefits and risks of this therapy in an unfortunately largely growing number of people with T1D. Thank you all.

DR. BURMAN: Thank you. Will the next speaker step up to the podium, please, and introduce yourself? And state your name and any organization you are representing for the record.

DR. RODBARD: Dr. Burman, members of the

committee, ladies and gentlemen, my name is Dr. Helena Rodbard. I'm an endocrinologist in Rockville, Maryland with over 40 years of experience as a practicing physician. I have previously served as president of the American Association of Clinical Endocrinologists, the American College of Endocrinology, and as a principal author of guidelines for the treatment of diabetes. I'm here today speaking as an individual with no financial support from any source. I'm here representing by patients.

I was previously at the NIH conducting both clinical and basic research related to diabetes. I have conducted more than a hundred clinical trials related to diabetes and have been an author of 130 manuscripts in the peer-reviewed medical scientific literature.

I've had the opportunity of conducting several randomized-controlled clinical trials with SGLT2 inhibitors, including canagliflozin, dapagliflozin, and sotagliflozin in patients with type 1 diabetes. The SGLT2 inhibitors are a very

important class of drugs that's rapidly becoming the standard of care because of their consistent and well-documented cardiovascular and renal benefits.

There are many critical unmet needs in the management of people with type 1 diabetes. The only currently approved medications are insulin and pramlintide, both with significant risks for hypoglycemia. Only a small percentage of patients achieve the target levels for hemoglobin A1c recommended by the ADA to reduce the risk of serious micro- and macrovascular complications of diabetes and with the low risk of hypoglycemia. There is a critical need for additional forms of therapy to be used combined with insulin.

I would like to share my experience from randomized placebo-controlled clinical trials of SGLT2 inhibitors and from my personal experience with SGLT2 inhibitors and off-label use in people with type 1 diabetes. The benefits that my patients obtained with the use of these drugs included improvement in hemoglobin A1c levels; less

glycemic variability; increased sense of general wellbeing; and improved satisfaction with treatment. As an added bonus, there is some weight loss, reduced insulin doses, and reduced risk of hypoglycemia.

In my opinion, the benefits of SGLT2 inhibitors used in conjunction with insulin, in patients with type 1 diabetes, greatly outweigh potential risks. The risks of DKA can be greatly reduced by appropriate patient selection, education, and clinical management. I had the opportunity to participate in a consensus conference to develop methods to mitigate the risk of DKA in people with type 1 diabetes. The proceedings of this conference were recently published and provide a framework for patient care.

In view of my very positive experience with several SGLT2 inhibitors or SGLT2 and SGLT1/2 inhibitors in the treatment of people with type 1 diabetes, I hope these drugs will be approved soon. Having FDA-approved SGLT2 inhibitors would be of great benefit to many of my patients and to

patients elsewhere. Physicians would no longer have to prescribe these medications off label, and patients would be more likely to have access and insurance coverage. Thank you very much for your attention.

DR. BURMAN: Thank you. Will the next speaker step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. KURIAN: Good afternoon and thank you to the chairperson, committee, and FDA for the opportunity to speak on this important issue for people with diabetes. My name is Martin Kurian, and this is Rhea Teng. We're speaking as representatives of Close Concerns, a healthcare information company that aims to improve patient outcomes by bridging knowledge gaps in the diabetes ecosystem. For disclosure, multiple for-profit and nonprofit organizations in diabetes subscribe to our fee-based newsletter called Closer Look, including empagliflozin sponsors.

At the core of today's debate is the

question of whether the risks associated with SGLT2 inhibitors outweigh their benefits. Given the elevated risk of diabetic ketoacidosis that has been seen across many of the trials in people with type 1 diabetes and the baseline risk of DKA in people with type 1 diabetes not taking SGLT2 inhibitors, the question might now be how to appropriately manage the risk of DKA in clinical practice.

To this end, multiple protocols have been developed with the aim of minimizing DKA risk. Our literature search has identified at least six such protocols that have been developed in recent years. The STITCH protocol published in 2018; an international consensus document published in 2019; the Stop DKA Protocol published in 2019 and an unpublished protocol from endocrinologist Dr. Anne Peters; the EMA product information for dapagliflozin and sotagliflozin in Europe; and the United Kingdom NICE guidance for dapagliflozin also contain specific guidance to minimize DKA risk.

Each of these protocols is referenced in our

submission to the public docket. We have examined these protocols and identified what appeared to be the most pressing areas of consensus and difference divided into three categories. Patient selection, management of SGLT2 inhibitor usage, and management of DKA.

MS. TENG: Regarding patient selection, one of the most relevant questions is whether or not a higher BMI decreases risk of DKA. Both the EMA indications for dapagliflozin and sotagliflozin require a BMI of greater than or equal to 27 kilograms per meter squared. While the dapagliflozin data seemed to support this BMI cutpoint, the sotagliflozin data is not as convincing.

Dr. Anne Peters has specified a minimum BMI of at least 21. Dr. Peters has also emphasized the importance of a baseline A1c requirement of below 9.0 percent, a selection criterion not included in any of the other protocols despite research showing that a higher A1c is associated with greater risk of DKA.

Similarly, a specific insulin dose requirement of 0.5 units per kilogram is only identified in the NICE guidance on dapagliflozin. While other protocols and thought leaders have specified low insulin need as an exclusion criterion for using an SGLT2 inhibitor, little work has been done to identify a set threshold.

In terms of drug management, the use of urinary or blood ketone monitoring is another choice that needs to be made. It's widely accepted that blood ketone monitoring is the more accurate method of testing, but its requirement can pose as another cost barrier for patients.

The Stop DKA protocol is the only protocol to maintain that blood ketone monitoring is the only method that should be used, while other protocols find either method to be acceptable but generally prefer blood ketone testing.

Furthermore, the frequency of routine ketone checks has not been formalized. Generally speaking, the various protocols state that ketone monitoring should be done either as a matter of

routine or in an individualized manner.

When treating ketosis in DKA, protocols deviate between ketone checks every 2 to 4 hours. It's understood -- [inaudible - mic fades] -- but we find it imperative to generate the data to enable patients and practitioners to have at least a baseline frequency for ketone measurement.

While we sincerely believe that empagliflozin and SGLT2 inhibitors more broadly may have the potential to profoundly benefit patients with type 1 diabetes, it's clear that greater research into how these drugs can most safely be implemented is needed.

Moving forward, we hope to see data regarding these various points of difference so that evidence-based strategies can be put into place to minimize the risk of DKA. Thank you very much.

DR. BURMAN: Thank you both. Will the next speaker step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. TAYLOR: My name is Simeon Taylor. I am a professor at University of Maryland. When I was vice president of cardiovascular and metabolic disease research at Bristol-Myers Squibb, I contributed to R&D, leading to the approval of dapagliflozin. I retired from BMS six years ago and no longer own any pharmaceutical company's stock.

I was going to start with talking about the safety of empagliflozin 2 and a half milligram dose, but having sat through the FDA analysis, which was striking for its clarity, eloquence, and scientific rigor, I would just like to underscore some of the points they made.

No doubt, 2 and a half milligrams is safer than the higher doses, but that doesn't mean it's safe. It's clear that 241 patients for 6 months is not a sufficient safety database for a drug that's going to be given for 10, 20, or 30 years, and all of the concerns and limitations they identified in the classification of ketosis and ketoacidosis patients I think are really important to keep in

mind.

I draw the conclusion that it's really premature to make any inferences about the safety of this dose other than it probably is safer than the higher doses. While the data may not rigorously prove it causes ketoacidosis, it clearly doesn't exonerate the drug in that regard. I must say, having gone to a number of advisory committees over the years, I was particularly struck by the high quality of the FDA's presentation today.

So I'd like to ask a few questions that I think need to be addressed. The first question is will glycemic efficacy be sustained beyond 6 months? These are data from a review article we wrote that recently came out in Lancet Diabetes and Endocrinology, and this plots the drug associated decrease in A1c over time.

Now, please note, this is not the A1c per se; it's the drug effect. It's the delta. So you will see that the maximum delta is seen at about 8 weeks, and it's on average about 0.6 percentage points. The A1c lowering wanes over time, and

between 26 weeks and a year, the decrement is somewhere in the range between 0.1 and 0.15 percent. So if you start with a 0.26 percentage point decrease, at the end of the year, if it were to follow the same course, you'd only be left with about 0.1 to 0.16 percent. [Inaudible - mic fades].

DR. BURMAN: Dr. Taylor, your microphone doesn't seem to be on.

DR. TAYLOR: It has been on -- [inaudible - mic fades]?

DR. BURMAN: Yes, up until now.

DR. TAYLOR: Thanks.

In any case, if the same decrement occurred, starting with a 2.5-milligram dose at the end of the year, the residual A1c lowering would only be between 0.11 and 0.16 percent, and I think that's food for thought.

We wondered what caused this decrease with the waning A1c lowering, and one hypothesis that we included in our paper is that it's well known that glucosuria causes calorie loss, the body senses its

calorie loss, and it's known that after around 20 weeks or so, there's an increase in food intake. And we wondered if these type 1 diabetes patients are increasing their food intake, whether that can contribute to the decrement in A1c lowering.

I did, however, over the past week, actually, while preparing for this, come up with another thought about what might cause it, and I would like to share it with you because I do think it's potentially important. It's known -- and this has been known for decades -- that the hemoglobin molecule is not glycated when it's first synthesized, but undergoes chemical reaction with glucose over time as the red cells age.

This is a graph showing erythrocytes from a type 2 diabetes patient, and the erythrocytes are fractionated by age with young red cells on the left and the old red cells on the right. You'll see that the young red cells on average have an A1c of about 4 percent and the old ones have an A1c of about 13 percent, and the total blood is a reflection of the average. But we know that

empagliflozin increases the hematocrit. This was reported by in N. Suzuki [ph] and others with data from the EMPA-REG study; and further, Ferrannini and others have shown that empagliflozin increases erythropoietin.

Erythropoietin, of course, stimulates the creation, the production, of new red blood cells, so that would necessarily decrease the average A1c, but that's completely unrelated to glucose levels in the body. That's a non-glycemic artifact, in a sense, that's causing the A1c to seem lower than it seems to be. It would probably take months, based on the 120-day lifetime of a red cell, to achieve a new steady state.

So I submit that the A1c at 26 weeks probably overestimates the actual change in glucose lowering, but rather the one-year data may be more reflective of the change. So I think caution should be exercised before interpreting this decrease at 26 weeks as significant.

The last thing I'd like to talk about is the question of whether the modest possibly transient

glycemic efficacy will be translated into approved clinical outcomes. These are data from DCCT, and you'll see that there's a striking decrease in A1c in that study as a result of intensive insulin therapy of about 2 percentage points, and this is sustained over 10 years. You can see it's really well sustained. So it takes a huge leap of faith to extrapolate from these data to the EASE-3, where you have what's possibly a transient and much smaller A1c lowering.

Also, I want to emphasize, shown on the left, that in the DCCT study, in the first two years, improved A1c actually accelerated the progression of diabetic retinopathy; and in the right, it took 3 to 5 years to actually slow the progression of albuminuria.

So I think it's really critical to show whether the 2.5-milligram dose of empagliflozin will actually sustain for at least 3 or 5 years to have the ability to really believe it's going to have a beneficial effect on clinical outcomes.

I think I'm sort of going over time because

I deviated from the script, and I won't go through all of this. But I do want to emphasize I don't really believe that the current data package proves that the benefits outweigh the risks. I think it's really important to show that the A1c reduction will be sustained and to see how much it will be. And I would recommend placebo-controlled studies of at least three and possibly five years would be helpful.

Also, I think we should understand that the clinical profile depends only, in part, on the drug, but it depends critically on this skill of both the patients and the physicians to manage the insulin, and it's really far from clear that even the results that have been reported in the clinical trial would be replicated in real-world practice, so thank you very much.

DR. BURMAN: Thank you, Dr. Taylor. Will the next speaker step up to the podium and introduce yourself? Please state your name and any organization you are representing.

DR. WOLFE: I'm Sidney Wolfe, Public

Citizen, no conflicts of interest. Serious problems preclude FDA approval, at least thus far, of empa, sota, and dapagliflozin. The FDA, after the advisory committee meeting in January, turned down sota, and without an advisory committee turned on dapa; and, obviously, the data from the 10- and 25-milligram trials with empagliflozin were not thought by the company to mirror approval, and so they've not sought approval.

The three serious problems I just want to briefly describe are, one, that the surrogate marker, or the hemoglobin A1c, improves maximally, and it is true with all three of these drugs, including the current one, between 4 and 12 weeks after starting therapy, but then starts worsening, continuing to do so for at least one year.

In the case of the full year, which we do not have, as mentioned by many people, including the company -- we don't have a full year for the 2.5. But in the ones where there is a full year, the difference between the maximum at 4 to 12 weeks in the end is it loses between 30 and 50 percent,

or more in one case, of the benefit. In other words, the benefit disappears at a fairly steady rate and could even disappear longer than that. There are no trials published with data more than one year.

Secondly, the ketoacidosis, which was described, including by me and others, as the elephant in the room in the sotagliflozin study, the life-threatening harm caused by these drugs can occur less than 3 weeks after therapy begins. You've seen the slides of incremental increases in DKA, going all the way through the time that the drug is given. The plateau in the end of those graphs are after they stop taking the drug.

So you essentially have the harm benefit ratio getting worse over time because the benefit decreases after the first 8 to 12 weeks, and there's a continuing risk, and it would probably continue longer than a year if anyone had any data for that. So thus, the harm benefit ratio soon becomes unfavorable for patients with continued occurrence of life-threatening DKA but decreasing

benefit.

The last thing, which has been alluded to a number of times today and at the meeting in January, is the question can a better risk reduction program, than was done in the clinical trials and to any of them -- this one, the sotagliflozin, the dapagliflozin, is it possible to do better than what's going on in the clinical trials? Whereas people have put up protocols and published articles, if you look carefully at them, they have mainly the same kinds of information that were used during the clinical trials.

The one most disturbing thing about that is the real-world evidence that was presented by the FDA at the meeting in January from the Sentinel data. What it showed was that for empagliflozin and for dapagliflozin, the risk ratio was 6 extra cases of DKA per hundred patient-years, which is higher by a significant amount -- there are a lot of adjustments that have to be made and were made already -- that you would get in the clinical trials.

So common sense would have it that with the variety of doctors and the variety of patients in the real world that would get prescribed these drugs, including the 2.5 if it ever got approved, you're going to do worse, not better. And as the FDA pointed out in January, there is no evidence of any kind of risk modification program that's ever been tested. Therefore, to say, oh, well, let's approve it and do the risk modification afterwards is I think irresponsible.

Just to briefly go through the first point I made, which is the risk reduction, the decrease in hemoglobin A1c being evanescent, again, even in the 26 weeks, it went down maximum at 4 weeks, and by the time you got to the 26 weeks, it had gone up a significant amount. There's no reason to think, from the other studies that did go longer, that this would not continue. For example, in both sotagliflozin and dapagliflozin, the peak was anywhere from 4 to 12 weeks, the peak benefits, so to speak, of hemoglobin A1c, and by the time you got out to 52 weeks, you had lost 30, 40, 50

percent of it.

One of the other things that's clear is that in the second half a year in the other trials, sotagliflozin, for example, more than half of the cases of DKA occurred in the second half of the year on the 200-milligram dose.

You've already seen some of the data with the ketone-related events. If you look at all of the events that I think need to be looked at in terms of risk, you see an almost statistically significant increase at the 2.5-milligram dose compared to placebo in, again, just 26 weeks.

As Dr. Taylor said, I was surprised to see the important depth to which the FDA went to try and raise serious questions about the validity of the adjudication process, knowing, for example, that the patient who died was not classified as having definite DKA.

In summary, the vote, I think it is not reasonable that this drug be approved because there is no evidence, no significant evidence, plausible evidence, that the benefits, even if they are the

0.28 over 26 weeks, outweigh the risks because the risks are not clearly defined. It is not just the trial was underpowered with 241 patients or that it only continued for 26 weeks. There is the adjudication problem in terms of defining that kind of risk.

So given the tens of thousands of type 1 diabetes patients that are currently being prescribed off-label flozins with unacceptably high DKA rates, such as a Sentinel study showed, the FDA approval of the 2 and a half milligram dose, after larger doses of empagliflozin, sotagliflozin, and dapa have been found unimprovable or in fact were not approved by the FDA, may send a dangerous false green signal to those doctors who are already prescribing off-label SGLT2 inhibitors. And it may easily increase the idea of the false sense that we have found the sweet spot that was referred to by the company.

It's always nice in any disease to find a sweet spot where the benefits outweigh the risks. There is no evidence, at any dose, for this drug

that that's the case, and I cannot see how the FDA or the advisory committee would suggest approval.

DR. BURMAN: Thank you. Will speaker number 8, the last speaker, step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. ZELDES: Thank you for the opportunity to speak here today. My name is Nina Zeldes, and I'm a senior fellow at the National Center for Health Research. Our center analyzes scientific and medical data to provide objective health information for patients, health professionals, and policy makers. We do not accept funding from drug and medical device companies, so I have no conflicts of interest.

Drugs that help patients manage their type 1 diabetes and improve their quality of life would greatly benefit patients. However, it is not clear that this drug fulfills those goals. The data for the 2.5-milligram dose rests on a single phase 3 trial. As we all know, replication is the key to

scientific evidence. Independent clinical trials could have a smaller or larger effect due to the difference in the demographics or comorbidities of patients and other factors.

This is of particular importance here, as there was a lack of diversity in the study. For example, 97 percent of the 241 patients in the treatment arm were white. Although a subgroup analysis was performed on non-whites, there was obviously too few, 7 in the treatment arm, to have meaningful data about safety and efficacy.

Additionally, only about 30 percent of patients were enrolled in North America, and no numbers were provided regarding the number of patients in the United States. There are vast differences in obesity, eating, and drinking habits and other health habits such as smoking and exercise, as well as access to healthcare. Many of these variables could affect the risks and benefits of this drug for you as patients.

It is, therefore, not clear how applicable the data are for the U.S. population that the

sponsor seeks approval for. The trial was also a very short duration considering this is a drug that is expected to be taken for many years by patients. The long-term risks and benefits were not studied, so we don't know whether the benefits are likely to outweigh the risks long term. And while reduction of HbA1c is an accepted surrogate endpoint for these products, it is not clear if the small improvement seen in the clinical trial is clinically meaningful for patients.

It is also important to point out that patients in this one trial were much more carefully selected and monitored than they will be in the real world of medical practice.

There is no urgency to approve this drug given that there are so many unknowns. The mission of the FDA is to provide patients with real clinically meaningful benefits. As advisors to the FDA, it is essential that you speak on behalf of patients' safety and to carefully consider and weigh how this drug could harm or benefit patients. Thank you for your time.

Clarifying Questions to FDA and Applicant

DR. BURMAN: Thank you all very much. This closes the OPH session. Normally, with this schedule right now, is that we would go to the questions for the discussion for the panel. However, we do have some time to make up the questions that were raised this morning for the FDA or for the sponsor. We'll do that for about 20 to 30 minutes, and then go to the questions.

Dr. Yanovski?

DR. YANOVSKI: Thanks. I had a question for the FDA. Regarding the efficacy of this medication, I can't remember who mentioned a statement of noninferiority. I wonder if you'd just expand exactly noninferiority versus placebo or the higher doses, did you mean. What was your noninferiority statement there?

DR. GOMATAM: Sorry. I reviewed the safety, the DKA risk, not --

DR. YANOVSKI: It may have been Dr. Niyyati.

DR. YANOFF: Yes. I think we were trying to put the A1c reduction into context, noting that

when we review active comparator studies for diabetes drugs, the noninferiority margin is often set at 0.3 or 0.4 percent, which means that, in general, stakeholders believe that that's an amount of effect you're willing to lose to say a drug still works compared to something else; so here we have something that's smaller than that.

DR. YANOVSKI: Right. So this would be considered equivalent to placebo in terms of noninferiority? Am I stating that accurately?

DR. YANOFF: I would prefer my statistician colleagues to comment if that's accurate, but I think what we're saying is that in an active comparator study, if you were to lose 0.26 percent, you would say it's not statistically worse or it's within a margin that we're willing to accept that loss of efficacy and still say the product is effective.

DR. YANOVSKI: Right. So then, in general, the FDA requires more than one phase 3 trial for approval of drugs in general. Are there other examples for common disorders where the level of

evidence that's been presented today, short term, one big phase 3 with the relevant dose have approval?

DR. YANOFF: Without coming up with any specific examples, I think that, in general, that's within the legal framework, regulatory framework, that that can be acceptable as long as there's one adequate and well-controlled trial with either confirmatory evidence or supportive evidence that's convincing. We outlined the evidence in the clinical pharmacology slides about the other supportive evidence that we're using. I think our main question is, is it meaningful and how does it balance against the risks?

DR. BURMAN: Thank you. Dr. Chrischilles?

DR. CHRISCHILLES: Actually, my question was answered just before lunch by the answer to Dr. Brittain's question.

DR. BURMAN: Thank you. Dr. Meininger?

DR. MEININGER: Thank you. My question's more for the FDA about postmarketing incidence DKA. As was already noted by many, the available doses

for SGLT2 inhibitors are those that are much higher for type 2 diabetes, and there's quite a bit of off-label use. I believe earlier it was cited that 3 percent of type 1 diabetics are taking SGLT2 inhibitors.

Obviously, a lower dose, as shown today by the sponsor, while there may be some uncertainties about the specific rates, they're obviously lower. So I wanted to understand, from the FDA's perspective, what the postmarketing incidence is for DKA, because, presumably, a lower dose with lower risk would reduce that use.

DR. YANOFF: We looked at cases that are reported in postmarketing for approved products, but keep in mind they're only approved for type 2. This is really an exploratory study, and I'm going to invite Dr. Hampp up to explain to you what we did. One of applicant's presentations alluded to the paper. There's a reference to his paper in their handout.

DR. HAMPP: My name is Christian Hampp. I was the lead author on that study that was put up

by the applicant and most recently published in Diabetes Care. We looked at Sentinel data for canagliflozin, dapa, and empa for off-label use for type 1 diabetes, and we had two different diabetes definitions. One was narrow; one was broad. But I think for this discussion, the narrow definition is most important.

If I remember correctly, on average, we found about a rate of 6 per 100 person-years of DKA events, but that varies highly by age. So this average could be different in a different population at a different average age. The highest rates we found among women under the age of 44 up to 20 per 100 person-years. I cannot really comment on low-dose effects because these were approved as SGLT2 inhibitors that were used off label, so they are no low-dose ones.

Does that answer your question?

DR. MEININGER: Yes. Thanks.

DR. BURMAN: Thank you. Dr. Kalyani?

DR. KALYANI: Hi. I had a question for the sponsor in terms of ketone-related events. I was

curious. How many of those people that didn't have potential or certain DKA -- so in the unlikely DKA but ketosis or just elevated ketones -- may have eventually went on to evolve to potential or certain DKA?

DR. GEORGE: In fact, Dr. Kalyani, the conservative thing to estimate is that all patients with ketones between 1.5 and 3.8 could progress to DKA, and that's what was presented by Dr. Schorling earlier. Since there was a lot of discussion around adjudication, if I might take a few minutes just to inform the discussion about our clinical objectives and the criteria we employed, that might be helpful. Dr. Perkins can do that for us.

DR. PERKINS: Thank you. I have a lot of empathy for the discussion around classification that Dr. Niyyati spoke about earlier, the structure for the criteria for classification, and then the structure for adjudication. Also, we noticed back here that some of you were sort of Googling the difference between ketosis and ketoacidosis, and I understand that it's a difficult concept. So I

just want to take a few moments to provide some background.

People without diabetes make ketones all the time. It is the source of energy during fasting, and it's sort of mediated by lower insulin and higher glucagon. In someone with diabetes, we would expect the same variation in ketones, except it can be exaggerated if there are occasional deficiencies in ketones or excess in glucagon and other stress hormones.

We have a current surveillance bias, you could say, in that we only ask people to check ketones when they have high sugars and they have symptoms. But even people with more normal sugars and without symptoms have a large variability in ketone levels. The other fact is that these medications raise the average ketone by a small amount. Part of that may be the benefit, the metabolic benefit of the drug. This is the concept of ketosis.

Ketoacidosis is a decompensation, where ketones are high enough that there is acidification

of the blood, and the body's normal system for managing that acidity is decompensated. We call that diabetic ketoacidosis. Making this definition is complicated from a clinical standpoint. Maybe I'll just have slide 2 up.

This would be a standard definition for making a diagnosis of diabetic ketoacidosis. This is an example from the American Diabetes Association, and there are many other examples from consensus committees internationally. We applied these concepts. The idea is that DKA involves a decompensation from ketosis, so we need evidence of acidosis, which could be from a pH, a bicarb, and the presence of ketones, and generally, or an anion gap, I should say. So these are measures of the presence of a ketone or an anion gap, and then clinical manifestations.

We applied the principles of this kind of classification to the criteria with three modifications. The first is that because the mechanism of this medication could involve decompensation to ketoacidosis with more normal

blood glucose levels, we ignored the plasma glucose requirement. That's the first modification.

The second thing is we understand in clinical practice there can be missing data. So someone could have ketoacidosis, but through clinical management, a pH wasn't measured, for example. So in the absence of information, we want to be able to use other supportive information to classify someone as having ketoacidosis.

For example, if someone is missing a pH, we could use a bicarb or an anion gap to have a classification of ketoacidosis. However, if someone does not have a blood sample taken for pH -- I'm sorry; that's the situation I gave. If there is no blood sample at all, we could use supportive evidence. But if there is a blood sample and the result doesn't show acidosis, then that would be used to exclude.

Now, there are some exceptions to this. I think Dr. Niyyati showed a good example of that in one of the cases, that someone could come in with two conditions. She presented someone who had

alkalosis, so a high pH, so there was something else happening. I don't know in that particular situation, but something else was happening, a respiratory illness. And at the same time, there may have been ketoacidosis. I agree that it couldn't have been perfectly excluded, it may have been present as well; but, overall, it wasn't a simple diabetic ketoacidosis classification.

In other examples of misclassification --

DR. BURMAN: Excuse me. Please be a little succinct. We have other questions.

DR. PERKINS: Of course. I apologize.

DR. BURMAN: Please. No, no problem.

DR. PERKINS: So my key point is we used traditional criteria with some modifications, and the final one is just a detail about the bicarb, that most others would use a bicarb under 15. We essentially did as well, except we only exclude acidosis of the bicarb over 18.

Let's move to slide number 1. What we could do is assume that everyone who has a significant level of ketosis -- even though that might be

normal and not actually a clinically relevant outcome, assume that they could move on to actual decompensation and diabetic ketoacidosis. On this forest plot, it is the first effect measure, where anyone, even outpatients feeling well regardless of their clinical situation, has a ketone level exceeding 1.5. This would give the broadest definition.

What we see is a hazard rate ratio of 1.65. So, to me, this is the hazard rate ratio that is giving the broadest situation where we would have the most sensitive definition of diabetic ketoacidosis. Those are the key points that I wanted to make.

DR. KALYANI: Thank you very much for that background. I guess my question was focused on ketone-related events, if we have information on whether those people with that ketone above 1.5 did go on to evolve to ketoacidosis or certain DKA.

DR. GEORGE: Some of them did, and that's where you have the investigator reporting them as DKA. I think what we need to bear in mind is that

there are two sources of information going into that plot. There is the adjudicated events, as presented by the FDA, going into that plot, and every patient was given a ketone monitoring system, and they were capturing the values through electronic diary. So both those sources were actually pooled to provide that information together.

DR. BURMAN: Thank you. Ms. McCollister?

MS. McCOLLISTER-SLIPP: I actually have a couple questions about study design from both the agency as well as the sponsor. You'd mentioned, as part of the Q&A in the prior session, there was a brief reference to the DTSQ, and I forget the name of the agency staff that referenced it. There seemed to be some degree of dissatisfaction with that, and I was curious if we could explore that a bit more, or maybe if I misunderstood what you were saying.

Then, there were a couple of references to, I guess, secondary endpoints that were -- and I may get this term wrong, but it was something to the

effect of they were gathered outside of the study structure. I don't know exactly what that means; and, again, I may be misremembering the term that was specifically used.

Then, the third question that I have is in terms of like phase 3 trials, I'm a little unclear as to how it works. I thought that when a company or sponsor takes something into a phase 3 trial, that they negotiate or discuss what the trial design is with the agency. So I'm a little perplexed as to how we have application for a phase 3 trial with 240 patients. I was just wondering how that works and what exactly that process is.

DR. YANOFF: Our clinical outcomes assessment staff person had to leave, but she'll be back later to discuss the DTSQ if you'd like to get into that more later.

DR. BURMAN: Sure.

DR. YANOFF: The second question, you were asking about what it meant by outside the structure. That means outside the statistical testing hierarchy, so not controlled for type 1

error.

MS. McCOLLISTER-SLIPP: So does that just mean it's unreliable?

DR. YANOFF: I'm going to have to have my statistician come up and explain that to you, to make sure I don't say anything imprecise there, but not necessarily.

Then the last question, I think that the 241 is really -- we have a program that, after the fact, it was determined that marketing authorization would only be sought for the 2.5-milligram dose. So the 241 is really for that dose only. The larger program is sufficiently powered for a hemoglobin A1c outcome.

MS. McCOLLISTER-SLIPP: Thank you.

DR. BURMAN: Thank you. Dr. Brittain?

DR. YANOFF: We can explain to you what it means to be outside of a testing hierarchy or not controlled for type 1 error, if you'd like.

MS. McCOLLISTER-SLIPP: Sure.

DR. BURMAN: Sure.

DR. WANG: This is Yun Wang again, the team

leader for antidiabetic product development. We all know that a clinical trial may have a type 1 error, which means when we may find something by chance alone. So we always set aside a type 1 error, which is the alpha that we talk about.

Dr. Nason mentioned earlier that in EASE-3 studies, they only assigned 0.01 alpha for testing HbA1c for 2.5 milligram alone. They have not set aside any alpha for testing other secondary endpoints. That's what we are talking about. It means all those findings may be by chance alone. We don't know whether it's real or not. Thank you.

MS. McCOLLISTER-SLIPP: Then a couple of questions for the sponsor, similar. Is that possible?

DR. BURMAN: Yes, if they're quick, please. We certainly want to be inclusive.

MS. McCOLLISTER-SLIPP: Sure. I feel weird not addressing you, but you can't hear me if I do that. I just have questions about the study size and how you think that a phase 3 trial of 241 patients is sufficient to come up with an

indication.

Then secondly, I was intrigued that there was a lack -- or that there wasn't more, I should say, data using CGMs referencing time in range, since that, from the patient perspective, is one of the most beneficial aspects of this drug that's driving off-label use. Then similar to that, why aren't there more references to patient-reported outcomes in the data that was presented? There was the one use of the DTSQ, which is about treatment satisfaction, but that's not necessarily the same as quality of life.

DR. GEORGE: Thank you. Mr. Chairman, with your permission, I would like to answer those questions. Firstly, as Dr. Yanoff mentioned, these randomized-controlled trials, and as we acknowledged in the presentation this morning, we set out with an idea that 10 and 25 would be the dose and 241 was the number of patients at 2.5 add-on.

The reason why we feel that provides sufficient evidence for registration is the fact

that there was consistency of effect across three randomized trials. There was the EASE-2, as well as EASE-1, and J-EASE-1. Second is we've tried to model those results in the EASE-2 trial, where 2.5 milligram was not studied. And thirdly, there is a lot of information that we can borrow from other diseases, in this particular case, type 2 diabetes. We do know that empagliflozin 2.5 milligram gives 70 percent of the urine glucose excretion of the 10 and 25. So therefore, the biology is well known, and we can actually extrapolate that.

Your second question was -- if you don't mind repeating it, Ms. McCollister-Slipp?

MS. McCOLLISTER-SLIPP: I believe it was around why so little CGM data and data related to time in range, given the importance of that in terms of driving off-label use of this class of drugs; then why so little patient-reported outcomes in terms of quality of life.

DR. GEORGE: One of the challenges, really, about patient-reported outcomes in diabetes drug development is the lack of validated tools that was

mentioned by our FDA colleagues early this morning. We use DTSQ because that's been around for years and it's being used in the literature quite a bit, but there are limitations to any patient-reported outcome. This is actually an unmet need. We need to develop better tools together.

To your question about CGM, in fact, indeed, time in range is a true benefit for patients, and there was a workshop that FDA and patients did together around outcomes beyond HbA1c. In the long-attempt trial of 52 weeks, continuous glucose monitoring was done in every one and was indicated as part of that. But in the 2.5-milligram trial, it was a self-study only a proportion of patients went to. And I agree with you. If you were to do these trial designs today, unlike 4 or 5 years ago when CGM was still coming into range, we would certainly integrate CGM into that trial design better.

DR. BURMAN: Thank you. I'd like to note that, as far as I know, and if I'm wrong, that time in range is not a validated surrogate endorsed by

the FDA, but is something of interest. But the hemoglobin A1c is the issue raised with the questions as a more validated surrogate.

MS. McCOLLISTER-SLIPP: I think that's a perfectly valid point, but it is what is driving a lot of the off-label use, so I -- anyway --

DR. BURMAN: Of course. Thank you.

DR. GEORGE: Mr. Chairman, your point about HbA1c, there were a couple of questions this morning, or discussion, that we would like to provide some answers for that we promised after lunch. When would you like us to do that?

DR. BURMAN: Thank you. We only have about five more minutes --

DR. GEORGE: Okay.

DR. BURMAN: -- and we have three other questions. Could you answer that question really quickly, like in a minute?

DR. GEORGE: Yes, indeed.

DR. BURMAN: Thank you.

DR. GEORGE: So the key question is about the totality of benefits over time. Professor

McGuire, please?

DR. McGUIRE: In one minute. Darren McGuire, UT Southwestern Medical Center. A big conundrum in interpreting these data is extrapolating both the net clinical benefit of the observed changes not just in A1c but in body weight, and in blood pressure, and in other metrics of cardiovascular risk and microvascular disease risk.

We've heard several times today about the Diabetes Control and Complications Trial. Just to remind everyone, that was a roughly 1400-patient trial of patients with type 1 diabetes, young adults randomized to more versus less intensive control. The trial was conducted in 1983 to 1993, and, on average, the patients on randomized trial protocol had an observation period of 6.5 years.

Beginning in 1994, when that randomized trial completed, the investigators embarked on the EDIC study, and now in its 37th year of annual data collection of granular data -- and these data are now fed into the core type 1 diabetes model that

Dr. Perkins introduced earlier.

This is an annually updated model managed by IQVIA Data Solutions, and this core type 1 diabetes models is used for health technology assessment for health authorities around the world. This is the best type 1 diabetes model in existence. It takes not only the baseline data but annually updates and uses time variable, co-variable update analysis, so it changes, and the parameters can also be modeled.

So with that introduction, if I can have slide 1 up first, the sponsor in collaboration with a IQVIA Data Solutions has done some modeling to predict the clinical benefits of the observed changes, not only in A1c but also modeling changes in weight; changes in blood pressure, both systolic and diastolic; and changes in lipid parameters.

What you see on this slide are the relative risk estimates for risk reduction for individual micro and macrovascular disease complications. Fortunately, these data align very nicely with the projections from the FDA using these 6.5 year DCCT observed randomized trial period.

Understand that patients entering DCCT were, on average, 26 years old. So at 6.5 years of observation, we're talking about 32.5 years in a patient population that live with a lifetime of type 1 diabetes. The core type 1 diabetes model actually models outcomes throughout the projected lifespan of the patients.

What you see here is a projection of roughly 10 to 15 percent for each of the selected microvascular disease complications and ranging from 5 to 9 percent relative risk reductions for the cardiovascular complications, including atherosclerotic cardiovascular disease and heart failure.

If we can see slide 2?

DR. BURMAN: Well, there really is a time crunch. Could you just summarize?

DR. McGUIRE: Yes. So to summarize here, these are the projected per 1000 patient-years absolute total number of events prevented, micro plus macrovascular, totaling, as they add all together, 142 clinically relevant outcome events

prevented by the changes observed in EASE-3.

DR. BURMAN: Thank you. Let me outline the schedule. We definitely want to get to the questions and the panel discussion. We may have time for one more question to FDA or the sponsor.

Dr. Brittain, I think you were next.

DR. BRITTAIN: My question should be very quick. Maybe there will be time for another. Again, I'm still a little trying to understand about why the two phase 3 studies were done as they were. Obviously, if the second phase 3 study had had the 2.5 dose, I think we'd all be in a lot better place in understanding the risk-benefit of that dose.

So I just want to make sure I understand what was the history. Was the 2.5 not really recognized as the best dose until after the phase 3 studies were done; and that's why only the one short study had the 2.5? I'm just trying to understand, and I'm also wondering what the FDA advice was at the time that these would were designed.

DR. YANOFF: I believe you're correct. I don't want to speak for the company about their business decisions, but the 10 and 25 are approved for type 2, and that was what they believed would work for type 1. The studies were already designed, but when we met with you, it was around the time that the signal was emerging of DKA, and we advised the company that they should look at a lower dose.

Now, why 2.5 specifically was selected and not 5, I actually don't really know. And why the 2.5 was only added to one of the two trials, I don't know. But I believe what I heard this morning was that they really were not expecting the trial to read out the way it did and really to be applying only for the 2.5 for approval.

DR. GEORGE: If I might just add a sentence, Chairman, to what Dr. Yanoff said of 2.5 only and the dose selection, slide 1 up, a please? This slide shows empagliflozin in 2.5, 5, and 10 milligram all plotted across an exposure-response here. Our intention was to

select a dose that is distinctly different from the 10 milligram, and as you can see if we go up to 5, it will be too close to 10, to Dr. Yanoff's point.

Mr. Chairman, there were a couple of other questions about net benefit-risk, and we have done a calculation. I don't want to interrupt the proceedings, but we can come back to it later if you have to.

DR. BURMAN: Well, we do have to move on, but, obviously, that's important. This time, could you do it really in a minute?

(Laughter.)

DR. GEORGE: I will have to start where Dr. McGuire left it. That is BU-407, please, and, obviously, we had to start with the benefits of patients. This is the totality of benefits that we've modeled our patients' life-years. So we tried to do the same on the risk side to see whether this would come up. We made two further conservative assumptions.

One conservative assumption we made was that everybody with 1.5 or more of ketones could

progress to DKA. In clinical reality, we know patients can self- treat or take insulin or carbs to fix that. The second conservative assessment we made was that patients would stay on drug despite DKA. And again, the clinical reality, we know that's unlikely to happen.

I'm trying to be succinct in the one minute that Mr. Chairman has given me. Slide RR-1 up, please. This shows the 142 clinical events prevented that Professor McGuire has mentioned and the possible number of events over a lifetime with the two assumptions that I mentioned.

It could be up to 23 events. My statisticians, like Dr. Yanoff, I need to rely on them. They tell me this is consistent with the summary slide that was presented as exploratory benefit results met by the FDA. The difference here is this is expressed in 1, 000 patient-years over the lifetime, like Dr. McGuire said. The other one is a 6.5 year estimate, and only going up to 6.5 years. Sorry; 10,000 patient-years calculation going up to 6.5, whereas here it is

1,000 patient-years so you can get a like comparison.

Questions to the Committee and Discussion

DR. BURMAN: Thank you very much.

There are other questions, but maybe they will come up in the discussion session. The committee will now turn its attention to the task at hand, the careful consideration of the data before the committee as well as the public comments. I would like everyone to participate, to the extent possible, voting and nonvoting members. We want everyone's opinion.

Let me give you an outline of the time schedule. It's around 2:15 now. There are three questions before the voting question. We'll spend a half an hour on each. If that works out, then we'll have a 15-minute break from 3:45 to 4:00, and then from 4:00 to 5:00, we'll take the time necessary for the voting question and ask everyone in the panel for their explanation of the voting question.

If that meets with your approval, let me

read the first question. Discuss whether empagliflozin 2.5 milligrams, as an adjunct to insulin, provides benefit for adult patients with type 1 diabetes. Discuss your views of the clinical meaningfulness of the small A1c reduction, as well as other endpoints studied to evaluate benefits of the empagliflozin 2.5 milligrams, including body weight and blood pressure.

The floor is now open for discussion, and as I said, we'd really like to encourage everyone to make a comment.

Ms. McCollister, you first.

MS. McCOLLISTER-SLIPP: I think this evidence and evidence that we've seen from other sources -- and I know that we're just supposed to focus on the evidence presented, and there are good reasons for that. But there are definitely benefits, and clinically meaningful benefits, to this class of drugs, specifically. I think that was sort of demonstrated in the data that was presented, but probably not as well as I would like.

In terms of the clinical meaningfulness of the A1c reduction, it's meaningful. It's not what would drive somebody like me to take this medication. The stuff that isn't under direct consideration are the things that would drive somebody like me to take this medication, which, again, I just think speaks to the inadequacy of hemoglobin A1c, but that's a different discussion.

I think that there are significant benefits for this class of drugs that we've seen evidence of in the data presented; otherwise, people wouldn't be assuming the risk of DKA to be able to take these drugs. Weight reduction and blood pressure and kidney disease are also significant concerns for type 1 patient that I don't think get as much attention as needed.

DR. BURMAN: Thank you. Dr. Newman?

DR. NEWMAN: After reviewing the data and listening to the presentations, I feel that this database on the dose of 2.5 milligrams is too small and too short of a time period to even know what the efficacy in terms of glycemic control may be.

The reported reduction of 0.26 may not actually be clinically meaningful, in my opinion, and that may not be what would happen at year 1 or year 2. It might be lower. So I am not certain about the clinical benefit with A1c reduction.

Also, there was reduction in systolic blood pressure, which was, I believe, an exploratory endpoint. Then there was a small reduction in weight, but I don't believe it was anywhere near the 5 percent reduction in weight that is used to determine whether medications for obesity will have a significant effect in reducing the comorbidities. I think it's very small.

DR. BURMAN: Thank you. Dr. de Lemos?

DR. DE LEMOS: I would agree. I would say the clinical meaningfulness of this small reduction is completely unclear. To extrapolate 100 person-years of follow-up to many years of follow-up in DCCT and EDIC is not appropriate. We have no idea what the durability of this is and what the clinical translation is. And when balanced against the safety concerns that are also

unclear, it's not nearly enough evidence, in my opinion, that the drug has clinical benefit.

DR. BURMAN: Dr. Pai?

DR. PAI: Majunath Pai, University of Michigan. Again, I think during the public hearing, Dr. Taylor, gave a pretty eloquent presentation, and I concur with a lot of the comments that were presented in that slide deck. I think the effect is very small. It's not durable. It's wedged on the placebo going higher, basically. The delta is only 0.05 at 26 weeks and is likely to be much lower at 52 weeks.

There's a lot of information in the briefing document that was not discussed, potential differences based on sex, perhaps, sex-related differences; individuals with low GFR, estimated GFR. There's not enough data in those populations either. Most of the population was Caucasian, again, so there's not enough data in other specific populations.

DR. BURMAN: Thank you. Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I would

agree. I think that the magnitude of benefit is small in both A1c lowering, as well as weight reduction and blood pressure lowering, and there no impact on severe hypoglycemia. I think the durability is really the biggest question. With the small magnitude of benefit, we need to see how long this is going to last.

DR. BURMAN: Thank you. Dr. Kalyani?

DR. KALYANI: Yes. I also agree that the A1c reduction is relatively small, and while on par with pramlintide, which is the only other adjunctive therapy currently approved, that's a therapy that's not really widely used. The evidence presented to date doesn't demonstrate whether this A1c reduction would be sustained beyond 26 weeks, and that's where I think the uncertainty still remains.

DR. BURMAN: Thank you. Dr. Everett?

DR. EVERETT: Yes. Brandon Everett. With respect to the benefits, I want to emphasize that I see a very real clinical need in patients with type 1 diabetes that's a large population with

substantial morbidity and risk of mortality. There are limitations in the therapies that are available. In spite of that comment, we're now asked to make a decision about the benefits based on 240 patients treated for 26 weeks, which, given the stakes, seems like not a lot of information.

I think with respect to the hemoglobin A1c C reduction, I think 0.3 percent seems something that I would be willing to consider is clinically meaningful, and I think the right way to look at it is the placebo adjusted or placebo subtracted results. I know that's been somewhat of a topic of conversation.

I think the key features for me -- and these are not ones that necessarily gain you approval as clear surrogate endpoints -- is the fact that you can treat hyperglycemia without necessarily increasing the risk of hypoglycemia is an important adjunctive benefit of these therapies, in particular, postprandial hyperglycemia and other things that as a cardiologist without much detailed knowledge of this, as I understand it, can drive

risk both for macro- and microvascular events.

Then finally, I have friends whose children have type 1 diabetes, and the amount of time they spend worrying about time within the therapeutic range is on the verge of obsession. So I think that while that, again, is not a surrogate endpoint that might merit the FDA's attention at this point, I think it's worth considering it in the future because that is clearly what drives a lot of their alterations in insulin use, and changes in pump dosage, and all sorts of concerns for these people.

I think that if you could potentially find an adjunctive therapy that would enhance time within therapeutic range without increasing the risk of hypoglycemia, that would be a valuable addition to the therapeutic armamentarium.

DR. BURMAN: Thank you. Dr. Munir?

DR. MUNIR: As somebody who treats people with type 1 diabetes on a daily basis, I think reducing the hemoglobin A1c without increasing the risk of hypoglycemia is often a big challenge. I do think even a small 0.3 percent potential

decrease in hemoglobin A1c is clinically important. The question, I think, becomes durability of that change.

This was one of my questions, but maybe we can get to this later. As far as other endpoints, I would like to see the time in range difference, like does that change over time or is that sustained, because that could actually be important. The second thing is if it's one hour per day and that's persistent, that's 365 hours per year, which if my math is correct, is about 15 days of being in range, which is a half a month of being in range during the whole year, which actually does seem like a fair amount of time to be better controlled.

So I don't know if there's representative data of CGM curves or if there's data on greater than 250 just to see if we're taking the top off of these severe hyperglycemias that we could potentially see later. But I think, although it's not a validated measure, there are emerging data on time in range, and retinopathy, and some of these

microvascular complications. I think it is an important question and something that clinically we see all the time, and what's been mentioned, and that patients really find very beneficial.

DR. BURMAN: Thank you. Ms. Lellock.

MS. LELLOCK: I think there's definite benefit to this drug. As type 1 diabetics, we try really, really hard to get in range and to decrease all these parameters. But I do have concerns over the obvious potential increase in DKA, and I'd be interested in hearing about the other endpoints as well. So I think longer studies would be more beneficial, if that make sense.

DR. BURMAN: Dr. Meininger?

DR. MEININGER: Thank you. I just want to underscore some of the points that were already made and maybe add some additional ones. There's clearly an unmet medical need. I think all are aligned with that. Speaking not only as an endocrinologist but also an individual with type 1 diabetes, I can also comment on the tremendous amount of effort that goes into lowering A1c.

I think the effect that we're seeing here of about 0.3 percent is consistent, as shown by the sponsor, with available therapies, which are largely insulin, or modifications of insulin, or insulin delivery, and that there aren't additional therapies other than pramlintide. A1c I think is an important endpoint and is a continuous endpoint. It's doesn't stop at 0.3. Obviously, 0.5 would be better, but I think, long term, that's important to think about.

Then, there have been some comments about the duration of study. I would point out that in many type 2 diabetes programs, where a lot of these drugs and other classes of drugs have been studied, the placebo-controlled period, actually, is only 6 months. So what the sponsor studied in terms of an A1c effect versus placebo is not that distinct. Of course, it was in one study -- in one phase 3 study I should say -- but they did study it in other phase 2 studies and also modeled out the effects from a much larger database with higher doses.

DR. BURMAN: Thank you. Dr. Kalyani?

DR. KALYANI: I just wanted to make an additional comment that one of the things clinically that we often hope for when we add adjunctive therapy to people on insulin is a reduction in hypoglycemia. And while I appreciated that the time in range was increased by an hour per day, mostly because of the decrease in hyperglycemia range, and that there was no increase in serious adverse hypoglycemia in empa 2.5 versus placebo, it would have actually put the drug more in favor, even balanced with a smaller A1c reduction, if we had seen a reduction in hypoglycemia events, even given the relatively modest metabolic change.

DR. BURMAN: Dr. Brittain?

DR. BRITTAIN: First, I want to agree with Dr. Everett that the effect size that matters is the change from placebo. There may be some legitimate reasons why placebo is going up. If they were doing some kind of optimization during run-in, I can see how that might be happening.

That said, I do think the duration of the study being 26 weeks -- that's just a fact, it only went 26 weeks, and there seems to be some suggestion in the long-term study of perhaps a lessened benefit. I don't think we know. But that's the problem; we don't know. In terms of whether 0.3, 0.25, or 0.23 -- I mean, 0.3 or 0.25 change in hemoglobin A1c is important seemed all to depend on how you feel about the DKA risk.

DR. BURMAN: Thank you. Dr. Weber?

DR. WEBER: I just wanted to echo some of the comments earlier about the unmet need and the need to improve glycemic control, but not at the risk of hypoglycemia, so agents that can improve that. But I also wanted to put it in the big picture. We saw a slide earlier today about how additional interventions that are non-pharmacologic -- CGM, insulin pumps, and perhaps soon to becoming closed-loop systems -- can additively improve control. To my knowledge, they're not mutually exclusive. So I think understanding that in the big picture, and looking

at the potential benefits versus risks is really important.

DR. BURMAN: Thank you. Dr. Blaha?

DR. BLAHA: Thanks. Mike Blaha. Sticking to the question at hand on benefit -- and I'll certainly have remarks later about safety -- I agree, actually, with Dr. Everett, that the analysis for A1c lowering compared to placebo is the right analysis. I think that the 0.3, let's call it, is real and meaningful in my view. I think that's probably quite important. I don't treat type 1 diabetes, but I imagine that that's quite important. I think it's reasonable to make some projection of microvascular benefit with that.

Now, a few people have commented on the weight loss and blood pressure benefit, which I think it's consistent with what we know about SGLT2 inhibitors, and I think it's clinically significant as well in an additive way. I'm less concerned about the durability question.

Now, I'll come back to make several remarks, I'm sure, about the length of study as far as

safety. As far as the remark about studying A1c and how long one requires to make a durable measurement of A1c lowering, I actually found this persuasive. So on the benefit side, I think there are some clear benefits with the drug.

DR. BURMAN: Thank you. Dr. Pai?

DR. PAI: Majunath Pai, University of Michigan. Again, going back to this point if we're hanging our hat on this 0.3 reduction, in the pramlintide studies, the reduction was 0.5. The placebo was also a reduction of 0.2. So that delta was 0.3, but they're both going in the same direction.

This is the opposite. The placebo is going up and this going down and then going back up, so it is different. Even though we were talking about it as a 0.3 difference, it's not all the same. The placebos were going in different directions.

DR. BURMAN: Thank you. I'd like to make a few comments as well. As a member and chair of the panel, I really appreciate all the comments. Obviously, it's very controversial. I do agree

that there's an unmet need. As an endocrinologist, it's really a difficult question, is a 0.3 percent decrease in A1c meaningful?

The sponsor had a nice graph that was somewhat projected but indicated that there would be a significant decrease in microvascular complications with 0.3. If I understood correctly from this morning, several of the other agents that have been approved, mainly SGLT2 inhibitors, for treating type 2 diabetes, of course, had a hemoglobin A1c reduction in this same range of about 0.3 percent.

It's a difficult issue also because some of the speakers and some of the speakers in the open form suggested that a longer study would be necessary, and the question always is how long. A study of 2 to 3 years seems exorbitant and may be necessary, but it's always a balance of how many years do you do a study, does it project out, and could you have a reasonable time frame and then do a mitigation, a REMS study afterward, or another study after approval? That's always a difficult

question.

I would emphasize tremendously the importance of selection of patients regardless of whether you agree or don't agree with the hemoglobin A1c reduction. The article by Danne, at which Dr. Rodbard referred to and was on in diabetes care, was really instructive to me regarding the potential benefits and the potential risks, but really emphasized the importance of patient selection, and we can talk more about that later.

I would note as well, as in any study, clinical trial data may or may not be extractable to the real world. And I think in this circumstance, the patients were really highly selected, and there was a run-in period that selected them even further for a potential benefit. I'm not criticizing that; I'm just commenting on it. But the difference in the real world in terms of many aspects in patient care, and diabetic analysis, and following up on ketones, glucose management, and education of the patient and

physician are going to be very different.

However, I was impressed with the PK analysis from the FDA that indicated that the PK looked favorable to a large degree, and if I remember right, approximately 70 percent effective, if you will, compared to the higher doses of 10 to 25.

Does anybody have any other -- sure. Might you go first, please?

DR. NASON: I actually just wanted to respond to what Dr. Pai said because I think the problem with that is it depends on when you start the clock because of their run-in at the beginning. The sponsor had a slide at CC-37, where before the intensification, all the groups' average were up around 8.6, and by the time they started the drugs, they were down to about 8.1. So it just depends on which one you're calling times zero.

The reason I felt it was important to say something is because I wouldn't want the message to go back that for the next trial, they shouldn't do that, and they should start the clock before the

intensification, let's say. If they were to do that, it would make it look like both groups decreased, but you'd then have the mix of the intensification effect and the drug effects. It would be very difficult to untangle.

So I think they did it appropriately in that sense, and that's why it doesn't worry me that the placebo looks like it's trending up because it's trending up relative to their nadir, relative to the lowest they could get after the intensification, not relative to where they started at screening. That's all I wanted to add.

DR. BURMAN: Thank you. But of course, in the real world, there's no intensification period.

Ms. McCollister?

MS. McCOLLISTER-SLIPP: I just wanted to add one final note about the clinical benefit of that kind of an A1c reduction. I take a drug called pramlintide, which is the only other drug besides insulin, or class of drugs besides insulin that's been improved, and it had a similar A1c reduction.

I don't actually know that it reduced my A1c

at all, but I'm one of the few people that takes it because it's truly been a life changer for me. I was the first severe hypoglycemic -- unconscious hypoglycemia adverse event after it was approved. It has substantial risks, but the benefits far outweigh those risks, and the risks are things that I can mitigate. Now I've been taking it for a long time, but in the beginning I worked with my physician, we figured it out, and made it through.

So there are ways to mitigate very substantial life-threatening risks, and if the patient is committed to the kind of care and regimen they need, I think it's important to give them the arsenal of tools that could be available to them to be able to do that.

DR. BURMAN: Thank you. Any other comments? Yes?

DR. CHRISCHILLES: Betsy Chrischilles.

DR. BURMAN: Sorry. I should have mentioned it to everyone; I apologize. Please mention your name.

DR. CHRISCHILLES: Betsy Chrischilles,

University of Iowa. I'm an epidemiologist. I have been fascinated by the conversation about clinical benefit and am sympathetic to the particular unique PK/PD characteristics of this class of drugs. The one thing I'm not sure I have heard explicitly said in this round of statements is that we still only have one trial at this dose.

To me, with the inconsistencies between EASE-2 and EASE-3 for the other doses, that just kind of leaves an open question. Moving into the postmarketing arena, I'm pretty comfortable with observational data, but I would like to feel that that solid efficacy finding is there. So that's what is currently in my mind.

DR. BURMAN: Thank you.

Let me summarize, then, if there's no other question. This is obviously difficult, so, please, if you strongly disagree with this summary, let me know. I think there was active discussion regarding the impact of a small decrease in A1c, with some people saying it may have significant clinical impact, and it may decrease retinopathy

and nephropathy over time.

On the other hand, the A1c wasn't maintained or sustained for the whole -- that delta wasn't maintained for the whole period of time, and therefore it is unknown, over a longer period of time, whether the A1c decrease would be significant over a year, or 2 years, or 3 years.

The blood pressure, systolic and diastolic changes were minor. I yield to my cardiology friends and colleagues as to whether that is clinically meaningful. My understanding is it's small. It might depend on the time of day that it was measured, et cetera, but if that was maintained, that would be a benefit. The weight gain -- the weight loss was mild and may not be persistent over a longer period of time.

I think all of us agree there's only one phase 3 trial with a modeling analysis as well, and that longer studies over at least a year would be important if they were possible to be done.

Does anyone have any strong comments about that?

(No response.)

DR. BURMAN: Thank you.

Let's go to question number 2, which, again, emphasize that we'd love everyone to talk and give their opinion. The question is discuss your level of concern about the risk of DKA with the use of empagliflozin 2.5 milligrams in type 1 diabetic patients.

Discuss your level of confidence in the ability of the available safety database to accurately characterize the DKA risk given the small number of events observed in a single trial that is only 26 weeks in duration.

Discuss your level of confidence in the reliability of the adjudication process to assess DKA risk, including the clinical meaningfulness of the adjudication categories and the applicability of extrapolating risk management in a clinical trial setting to the real world.

Dr. Brittain will start it off.

DR. BRITTAIN: I don't think we have a really good idea what risks, if any, that the 2.5

gives for DKA. But what strikes me is, both, when they use the certain DKA as the endpoint or when they use the broader category with the three subcategories put together.

The upper end of the confidence interval was 4 for the relative risk or hazard ratio; for both cases, it was 4. That's what I'm thinking of. It is probably not that high. That would be like worst-case scenario, but because the database is so small, it's a big confidence interval.

DR. BURMAN: Ms. McCollister? And please say your name.

MS. McCOLLISTER-SLIPP: Sure. It's Anna McCollister. You'll get it by the end of the meeting, I'm sure, and you can drop the Slipp part. In terms of the risk of DKA, I think that DKA is a big risk as a clinical issue, but I don't know that this drug introduces that much of a greater risk in the relative scheme of things.

I have an insulin pump. Two years ago, I had a series of pump failures. I ended up in the ER with DKA twice. It was a very unpleasant

experience with long-term implications. It didn't mean I stopped using the pump, nor did it mean that the pump doesn't have significant demonstrated clinical benefits, both to A1c, as well as a whole bunch of quality-of-life measures.

So a lot of us live with insulin pumps. It's been a tremendous improvement, but there is a risk of DKA. Those risks are things that we have learned to mitigate through education, and understanding, and staying on top of it. Those are things that a clinician discusses with their patient when they have an insulin pump.

These are things that can be mitigated through discussion, and education, and risk mitigation. I think we need to keep that in mind. And again, to bring it home, two months ago, because I was trying to keep my blood sugar in range, I had a series of extreme excursions 2 times in one day from extreme high, like about 400, down to 40, back up, and ended up in the ER with supraventricular tachycardia, and was admitted in the hospital for a few days until the troponin

level dropped.

So that is a very significant, immediate risk of excursions, not just in terms of how functional I was, which, by the way, not very, but in terms of like the risk of immediate death, and that is all because of the impact of extreme excursions on my cardiovascular health.

These are very real risks that people are attempting to mitigate. That's what's driving the off-label use of this medication. So I would prefer to have those risks discussed through the doctor, with a doctor, with FDA's oversight, rather than just being used off label in the clinical setting where that risk isn't required to be studied, and observed, and mitigated.

DR. BURMAN: Thank you. Dr. Everett?

DR. EVERETT: Thanks. Brandon Everett. I have significant concerns about the risk of diabetic ketoacidosis, and in addition, other ketosis syndromes that are short of a full-on diabetic ketoacidosis. I think the vignettes that were provided, while not run the risk of being an N

equals 1 kind of approach to the problem, nonetheless give you a sense of the severity of illness and the seriousness of this as a category of adverse event, whether it's truly DKA or something short of that.

I think with respect to whether or not the database is adequate to really characterize the risk, I think the answer is no. I expressed some concerns about the adequacy of the database to characterize efficacy, which occurs in every patient and is a continuous outcome. So something that is much less common only happens to 15 patients in both treatment arms. I think you have to be left with the sense that it's not adequate to characterize that. Of course, that's the problem with adverse event reporting generally, is that there are infrequent events that occur out of the blue and are not consistently seen as efficacy endpoints.

To that point, I appreciate Dr. McGuire's comments earlier about specificity and sensitivity, in it being a balance when you're using an

endpoints committee. I run endpoints committees for large trials, and we're typically focused on specificity when we're interested in the efficacy endpoint. We're typically focused on sensitivity when we're interested on a safety endpoint.

So I think there's a fundamental difference in terms of how you look at those two events that occur in a trial population and how you ascertain them and how you adjudicate them. I think we've expanded the different definition, if you will, through the course of the discussion here, to broaden it beyond just purely adjudicated DKA. I think it's worth noting in some of the vignettes, the patients had pH's that were in the normal range, but that was, of course, after the ketosis had resolved and that kind of thing.

That brings me to my next point, which is that I applaud the sponsor for working so hard to protect the patients within the trial by giving them point-of-care monitors to look at beta hydroxybutyrate, but that is not going to happen in the real world. And from reading these vignettes,

again, it's very clear how much having information from that machine allowed patients and their care providers to manage the patients successfully and avoid serious adverse events.

So they were able to keep patients out of the emergency room, keep them out of the hospital because they could tell them to hydrate, check another ketone, et cetera. That's not going to happen, and that concerns me when you let the drug loose in a larger population of patients who are going to be less attuned than the highly selected group within the context of a clinical trial.

So I think there's a risk that rates of DKA, which are poorly characterized, are going to be much higher outside of the context of these trials. I think it's difficult to extrapolate what we've seen, with sparse data as they are, to any context outside of the 100 patient-years of active therapy in 100 patient-years of placebo therapy that we have in front of us.

DR. BURMAN: Thank you. Ms. Lellock?

MS. LELLOCK: I think there's a definite

concern over the risk of DKA in everyday life if you have diabetes. Like Anna said, our pumps could malfunction; we could miss a dose of insulin. So there's definitely concern over DKA in everyday life. It's definitely concerning as well that this could potentially increase DKA, but that's a risk we take all the time, anyway. I guess that's all I have to say about it, is it's a risk we're already taking.

DR. BURMAN: Sure. Thank you. Dr. de Lemos?

DR. DE LEMOS: In a trial that's efficacy outcome is a lab value that's modestly reduced, the safety profile has to be really clean to approve, based on small amounts of follow-up. This drug at this dose may actually be materially safer with regard to DKA than other SGLT2 inhibitors at higher doses, but we just don't know.

I think this is a promising first stab at this question, can you achieve some better glycemic control with a mitigated risk of DKA? I think that may be true, and there are some signals here that

are encouraging. But this is minimum of an order of magnitude too small; and the sample size and the duration of exposure have to be much larger because it's such an important question for all the reasons that Brandon and others have raised about the differences in the real-world application of this without serum ketone monitoring, as well as what will happen with longer durations of exposure, where you see this cam curve showing steady rates of DKA over time.

So I am optimistic about this dose. I'm just completely unconvinced by the data provided just because it's too small and too short an exposure period.

DR. BURMAN: Thank you. Dr. Weber?

DR. WEBER: This is Tom Weber. I'm also concerned about the DKA risk, and I just want to make a couple of points. One is we know, based on the available data, this is a class effect. This happens with all of the agents that have been studied in type 1 diabetes, and it's present in type 2 as well.

Now, there are dose differences, obviously, but when looking at the data -- and it was more apparent from the FDA presentations and from the sponsors -- there was discordance between the trials in terms of dosage and DKA risk. That raises the question that this may not be a purely dose-response relationship. So those give me pause.

Then I'll echo the other concerns about not being able to do this pragmatically in the real world, and I can see perhaps an increase in 4, or 5, or 10-fold risk if it's not done right. So that that's my concern in terms of the data.

DR. BURMAN: Thank you. Dr. Yanovski?

DR. YANOVSKI: All my points have been said. Thanks.

DR. BURMAN: Sure. Dr. Newman?

DR. NEWMAN: I agree with much of what has been said by my other colleagues on this committee. I am concerned about the risk of DKA with empagliflozin 2.5 milligrams, but I don't think it's been adequately assessed by this one study in

240 patients for 6 months. I appreciate the FDA's presentation, which I believe showed to me that the adjudication process did not err on the side of safety; that patients were excluded from having ketoacidosis when they probably did have ketoacidosis.

I'm also concerned that there were patients in this trial who were not even sent. Their records were sent for adjudication who might have DKA. And as we all know, extrapolating this to a real-world use, although I don't like the term "real world," will result in more cases of DKA. But I think there's room, I think this is promising, and I appreciate the work that the company, the sponsor, has done, and I think there is room to provide more data that would be more reassuring.

DR. BURMAN: Thank you. Dr. Kalyani?

DR. KALYANI: In terms of the level of confidence and the availability of the safety database, I really applaud the sponsor in seeing the need to monitor ketones ahead of time, and

having such a high compliance for patients and monitoring blood ketones 2 to 3 times per week on average after the first month. That being said, this study really represents the best-case scenario in terms of the number of DKA events that we will see, even given that high degree of motivation with the self-selected patients.

In real-world settings, again, using that term, we may not have patients who monitor ketones as regularly, even though there will be those that are very motivated. I also wondered, the ketone related events that were present, but not in the initial analysis but in the FDA subsequent analysis that showed unlikely ketoacidosis but ketosis, we know that ketosis and ketoacidosis are on a spectrum. Some have a greater degree or less degree.

So in this trial, people who were detected earlier on to have ketosis were given appropriate intervention, an education tool to hydrate. But what will happen in the real-world setting, and will they evolve to ketoacidosis? What will happen

during illness? I think these are the uncertain areas that will make it challenging for us to truly gauge the safety of this drug.

DR. BURMAN: Thank you. Dr. Blaha?

DR. BLAHA: Mike Blaha. I think we've had some outstanding commentary from the group. I agree with virtually everyone that's made comment so far. I think that almost for sure we have a non-zero risk of DKA with this. I think it is a class effect. I'm not convinced at all that sparing insulin is a good strategy. Even in type 1 diabetes, it seems like that just brings on more DKA. But I think almost surely the risk, though, is lower, of course, at the higher doses.

So there's this discussion of a sweet spot, but for now all I'm seeing is something that's a little less effective and a little less harmful, and the precision of that estimate is just completely unclear to me. I think we really don't have the precision to make a reasonable estimate of that trade-off.

So really, it comes down to the inadequate

safety database. I do think it's not on the order of -- we need a hundred more patients, and we need a lot more patients to really make that estimate. Unfortunately, we're way off, I think, what we need to really make that estimate.

I guess I'll echo what Dr. de Lemos said, which is that as a clinician and someone who wants great outcomes for patients, I do think this is promising. I think that's a good way of saying it, although I'm not sure we're here to evaluate promising things; we're here to evaluate proven things. But it is promising strategy.

DR. BURMAN: Thank you. Ms. McCollister-Slipp?

MS. McCOLLISTER-SLIPP: Just a final point about this issue, well, for now. And I also want to congratulate the FDA on their presentation. I thought you guys did a really good job of bringing out some important points that weren't apparent in the sponsor's presentation.

I think that this is one of many things recently that has highlighted our complete lack of

understanding, in a real way, of diabetic ketoacidosis in the real-world setting. It's not something that we're really focused on unless we get sick. Very few people actually measure it. I've never had a blood ketone meter. The strips are always expired when I need them.

I would love to see if there's a way that the FDA can do this or whether it's through -- I don't know if you have any mechanisms for doing this, but I would love to see this on some sort of new research into diabetic ketoacidosis because we clearly have a lack of understanding of how prevalent it is and what the implications of experiencing it might be.

DR. BURMAN: Thank you. Dr. Low Wang?

DR. LOW WANG: Thank you. Cecilia Low Wang. I also have a low level of confidence in the adequacy of the safety data, and just a couple of points. One is that I do think that that adjudicated category needed to be broader to include ketone-related SAEs, and there are plenty of people with mixed acid-based disorders out

there, so you can't go just by the pH.

I think the other thing is also the point about DKA with SGLT2 inhibitors. I don't think that we fully understand that, and that's been pointed out already. But over and over, I think we have all this evidence to show that we don't have enough evidence.

DR. BURMAN: Thank you. I'd like to make a few comments and agree with almost all of what the panel said and appreciate their critical comments. I also appreciate, of course, the FDA comments and the sponsor's comments.

To me, one of the major issues regarding this question is the difference between the clinical trial data and real life. Part of what I'm going to comment on is from the article in Diabetes Care by Danne. It emphasizes that the patient group should be very selective if you're using this drug in type 1 diabetes. They emphasize patient compliance and patient education, as well as doctor education.

If a patient comes into the emergency room

on these medications, they understand the pathophysiology and the patient willingness to comply and monitor closely ketones and glucose. I think ketones have to be measured in this circumstance, which adds extra costs; carbohydrate diet; ketogenic diets; and fasting diets all play a role.

The degree of hyperglycemia has to be considered. The future willingness to get pregnant has an issue on this. Surgery, illness, and, other systemic illnesses, obviously, have to be considered in the patient selection. Obviously, avoidance of alcohol, an appropriate A1c, I think we heard earlier less than 9, but less than 10 should also be considered.

I don't think we've talked sufficiently about patients on pumps. In the sponsor's presentation, if I remember correctly, approximately 40 percent of their patients were on an insulin pump. That's way more than my real-world experience, and I looked this up recently to confirm my suspicion in our discussion

that patients on insulin pumps have a higher risk of diabetic ketoacidosis, not because they're not compliant, probably, but because there's some problem with the pump. It gets interrupted or it gets kinked, something like that. And, of course, the patients and the physicians have to recognize the symptoms of nausea, vomiting, and of diabetic ketoacidosis.

So I agree that there's a stark difference potentially between the clinical trial and the real world, but maybe the truth is somewhere in between.

Does anybody have any other comments on this point?

(No response.)

DR. BURMAN: Then my summary will be -- oh, sure. Yes, please?

DR. CHRISCHILLES: Betsy Chrischilles, epidemiology from the University of Iowa. There were just two other points I was going to try to put in there that haven't been raised. One, I think we haven't specifically seen any evidence of the evidence base in support of the effectiveness

of risk management strategies. There are a lot of recommendations and variability among the recommendations and what should be done. But I don't think we know if they're effective at all.

But secondly, Dr. Hampp in his paper in Diabetes Care, did provide us with perhaps an upper bound of the diabetic ketoacidosis rates that we might have observed in type 1 diabetes, and it looked like it was about 80 percent higher. That would be expected based on clinical trial findings, and that was with the conventional doses of these therapies.

So that's a piece of information I think that we can think of in terms of an upper bound on the expected real rate in the real world.

DR. BURMAN: Thank you. Let me just ask the FDA on this question, are there any other specific issues you wanted brought up for discussion?

DR. YANOFF: Lisa Yanoff, FDA. None from me.

Anyone else from the FDA?

(No response.)

DR. BURMAN: Good. Thank you. Then my summary, again, open to your criticism and comments, is that, in answer to the specific question, the risk of diabetic ketoacidosis seems increased, and I think we all agree with that. The extent of increase is difficult to know, and there have been extrapolations, both for single patients and for populations.

The safety database, as we've seen from individual cases, was not particularly sensitive or not as sensitive as we would have liked regarding picking up patients with diabetic ketoacidosis in the trial, so it could have missed some or many patients in that regard. The adjudication process itself could be improved.

With regard to comparison to the real world, I think I just mentioned -- and so did the other group, other patients, other people, regarding some of the potential problems -- how much they influence the risk of DKA and other complications, as well as the benefit in the real world, versus the clinical trial is impossible to know. We could

just guess, and everyone can make their own opinion regarding the further questions.

Any further comments? Sure.

DR. MEININGER: Maybe just a clarification. I'm not sure I would --

DR. BURMAN: Please mention your name; I'm sorry.

DR. MEININGER: Oh, I'm sorry. Gary Meininger, industry rep.

DR. BURMAN: Thank you.

DR. MEININGER: I'm not sure I would say that the sponsor missed cases. I think they had to do with the categorization, and obviously they're more specific, and less specific, and more sensitive cases. I think even in the most sensitive analysis, the risk was increased. I think we all acknowledge that. The question is to what degree and how much data there is.

DR. BURMAN: Thank you.

DR. YANOFF: I would let the record stand with the original summary. I'm not sure I agree with your statement, but perhaps the committee can

debate further if there is disagreement there.

DR. BURMAN: I think we have a minute or two. Thank you for bringing that up, and thank you, Dr. Yanoff. I personally think that some of the cases that were presented were missed. Maybe a more appropriate way to say it is not appropriately categorized, but I would love the input of the committee.

DR. DE LEMOS: I would just say this isn't --

DR. BURMAN: I'm sorry. Please mention your name.

DR. DE LEMOS: James de Lemos; sorry. This is not a unique problem. If you looked at bleeding outcomes in an antiplatelet or antithrombotic trial, it's in the sponsor's interest to have a rigorous definition that's specific, when you know that the safety outcome is only going to go in one direction across all three doses.

I think in the future, the key is that the next series of trials designed to address the safety of this class of agents, along with what Dr.

Low Wang said, is they need to focus on clinically relevant, ketone-related events in a much broader panel, and then report secondary diagnoses within there. But the process of picking a tight definition of DKA will systematically underestimate the clinically relevant cases. It's not an adjudication problem per se; it's a definition problem.

DR. BURMAN: I agree with that. And I would emphasize, from my viewpoint, the sponsor did a reasonable job working with the FDA to try to give these categories, but now that we have the data, it may not have been sensitive enough.

Sorry. Dr. Yanoff?

DR. YANOFF: I thank everyone for discussing this point. I think it's very important. I think maybe it's the outcome of whether you have confidence in the data or not, rather than how we got there because while we didn't get into some of these details, we did find evidence that there were, perhaps, maybe one or two actual missed cases where information was in a CRF but not on the

adjudication worksheet, and then the case was not identified. But I don't want to sidetrack the discussion. I think that the point is the larger issue, whether the committee feels that you have confidence in the available data.

DR. BURMAN: Thank you all.

Dr. Newman, do you have a final comment on this topic?

DR. NEWMAN: Very briefly, I wanted to say what Dr. Yanoff said, that I think the FDA pointed out there were people in this study who may have had DKA because they had elevated beta hydroxybutyrate levels, but they weren't referred to the adjudication committee.

DR. BURMAN: Thank you. Let's go on to the next discussion topic. We'll spend 30 minutes on this if it works out, and then we'll take a break from three 3:45 to 4:00, and then come back for the final question and discussion after the vote.

Question number 3 or discussion topic number 3 is discuss the overall benefit-risk profile of empagliflozin 2.5 milligrams as an adjunct to

insulin therapy for the treatment of adult patients with type 1 diabetes. Discuss the sufficiency of demonstrated benefits in light of the uncertainties around the DKA risk and other risks of the drug.

Obviously, this is an important risk-benefit question. Dr. Blaha will start us off.

DR. BLAHA: Okay, great. I'll kick us off, and probably lots of good comments here. Mike Blaha. Well, I think there's been a lot of great discussion about the right patients, and I think clinically we can agree there are probably certain patients who are very good at self-care and monitoring self that might receive more benefit than other patients. Those patients might be more highly represented in the clinical trials, especially per protocol.

But I think the question for me is not the clinical question and are there certain patients who might benefit from this, but the larger question of the approval of this drug for this indication, can I confidently say that there's a net benefit of that? And I think based on the

discussion we've had and my comments personally, I'm not confident in that net benefit, particularly because of the lack of precision of the risks with this drug.

DR. BURMAN: Dr. Yanovski, please?

DR. YANOVSKI: I think that we actually have insufficient data on both the benefits and the risks of this drug because of the small number of clinical trial data points and virtually none more than 6 months. So I think we're really asked to approve a medication with inadequate data on both risk and benefit.

I do expect, actually, that this might turn out to be a very effective and relatively safe medication if it were adequately studied, but I really can't say that yea or nay.

DR. BURMAN: Dr. Brittain?

DR. BRITTAIN: I also am optimistic about this treatment. what I keep thinking is if the 2.5 had been included in that other trial and the results had been pretty much like they were in the other trial, that probably would be enough.

DR. BURMAN: Thank you. Dr. Munir?

DR. MUNIR: I think this is a very a tricky -- I think it's very balanced right now. Like I think Dr. Blaha said, there's less benefit and less risk. Even if we take all the DKA, going back to the risk issue, all the DKAs that were potential DKAs and all that, we do see a higher risk with empa versus placebo versus the data with the certain DKA. But even then it's less -- it seems very dose related, at least from the data that we have, and it seems like that's the case across all of the different drugs in the SGLT classes, in that class.

So it does seem reasonable the data that we have is probably the data that would be reproduced, but we don't know until it's reproduced. Again, the study duration is a little bit worrisome that it's only 26 weeks, and then the benefit, again, we see it there. It's just nice to see it replicated or maybe, like Dr. Burman said, how long, maybe one year or something like that.

So I think it's really right on the fence in

terms of where is the benefit and risk ratio here, for me. So I'll hear what other people have to say and kind of make a determination.

DR. BURMAN: Dr. Newman?

DR. NEWMAN: I want to say that I agree with what Dr. Yanovski said, and I don't think we have sufficient data to actually know the benefit nor sufficient data to know the risks of this therapy in patients with type 1 diabetes.

DR. BURMAN: Thank you. Dr. de Lemos?

DR. DE LEMOS: James de Lemos. I would agree with that, but having that second trial would not provide enough evidence there. So the next set of trials that are going to need to be done need to be materially larger to get a precision around the DKA signal. You can't do another 2[00]- or 400-person study of 2.5 milligrams and have any sense of what the risk is in the real world about DKA. So I agree with all that, but the next steps have to be much more rigorous.

DR. BURMAN: Dr. Low Wang?

DR. LOW WANG: Cecilia Low Wang. I think

right now we just don't have enough information to answer this question of benefit-to-risk ratio. I think there are uncertainties about the benefits, uncertainty about the risks. We don't really know who would best benefit and how best to mitigate the risk. So I would love to see a larger, longer trial, as well as more information about quality-of-life measures. Even though I know time in range is not a validated marker, I would love to see more of that as well.

DR. BURMAN: Thank you. Dr. Everett?

DR. EVERETT: Thanks. Brandon Everett. As James mentioned, I think that the sponsor's really trying to thread the needle here by finding a dose that offers some degree of efficacy while simultaneously minimizing the risk. I also agree that the data are promising in the sense that I think they've probably have found the right dose, and with enough clinical data, enough evidence, and enough patient-years of exposure, you're likely to see that this hemoglobin A1c reduction is sustained and consistent, and hopefully that the risk of DKA

and other ketosis outcomes is low.

I'm optimistic that that would be the case, but I think at present, we have a benefit, that while it seems to be small and is only based on observations in a small number of patients and a risk that is poorly characterized, unfortunately, it can be potentially severe and, as we saw, lead to death, and deserves to be better characterized.

I think with respect to managing that benefit-to-risk ratio, I think the sponsor's plan to market the drug separately, with a separate label, as a separate dose, is really important. I think that that's a key proposal that they've made and should be maintained going forward because I think that's important.

I also think that we're sort of living and dying by the hemoglobin A1c here, and I would just, without questioning the validity of that measure, raise the possibility that there may be other measures of efficacy that may be of interest to patients with diabetes, and those should be considered as potential secondary endpoints.

Coming from the world of type 2 diabetes and cardiovascular outcomes trials, I would also encourage the sponsor to think about other endpoints in this high-risk population that might be of particular interest such as nephropathy and renal outcomes, where while maybe not the first reason for approval, would be one that would be quite persuasive if the results were similar or parallel to what we've seen in patients with type 2 diabetes, albeit with a higher dose of the medication.

DR. BURMAN: Thank you.

Ms. McCollister-Slipp?

MS. McCOLLISTER-SLIPP: I have significant concerns about the application. I think the size of the patient population measured is borderline insulting as a patient.

Having said that, I think that this is a class of drugs that's currently being used by a lot of people off label. We don't have a very good sense of the risk of DKA in the general patient population. We certainly don't have a very good

sense of the risk of DKA in people who are using it off label because not that much DKA gets reported to the adverse events, and a lot of it doesn't even make its way into claims data. Even if we're looking at Sentinel data, there's significant gaps in it just because of the nature of that data and a way this stuff gets reported.

So I think, from my perspective as a patient/consumer, I think the real question that we need to consider is do we want people to take this class of medications without knowing what's happening and without having any kind of rigorous requirements on the part of the manufacturers to study it, and to track it, and to take responsibility for evolving the science. From my perspective, I think I would rather have that happen in a regulated environment where there is a degree of responsibility.

Secondly, if you don't have an indication, you don't get coverage. I take another drug, Victoza. It's a type 2 drug. I get lots of benefits in terms of glycemic variability. It is

really expensive, and because it is only indicated for type 2 but still used by a lot of type 1's, because of the indication for type 2, I was kicked off of it, summarily, a few months ago by my insurance company and had to engage in this really big fight. So I ended up getting it, but I spent six weeks with significant problems as a result.

My point is that we don't need the agency to create a stratification on behalf of people who can't afford and can fight battles with their insurance company, whether it's inadvertent or not. That is the reality of what happens when drugs do and don't get approved when we know that people are using them off label, is that some people who are wealthy or educated enough get access to medications that are paid for, and those who don't have wealth, or education, or access to people who can help lobby an insurance company, do not.

That's just the reality of living with this disease. I know the agency is limited by statute on what they can and can't decide on, and I certainly respect that, but these decisions don't

happen in a vacuum, and there are broader implications.

DR. BURMAN: Thank you. Dr. Kalyani?

DR. KALYANI: Hi. Rita Kalyani. In terms of the overall benefit versus risk profile, in terms of benefits, I think that the sponsor demonstrated the A1c lowering of 0.26 or 0.3 percent within the 26-week trial and was significant using all the different methodologies that the FDA looked at as well. Whether it's a durable decrease or not, beyond that, we can't extrapolate. But I think that's a question that we've already talked about.

There were secondary benefits in terms of blood pressure, decrease in weight, decrease in insulin dose, which for people with diabetes is important. As mentioned earlier, what would have been even more compelling as a benefit is if there was a reduction in hypoglycemia as well.

In terms of the risks, I think we still have uncertainty in terms of how significant this risk of ketoacidosis is. What is a ketone-related

event? What is ketoacidosis? These may just be semantics, but in the real-world setting, they can really become significant.

We also have uncertainty in terms of the implementation of the risk mitigation strategy. The sponsor did a tremendous job in educating participants in terms of ketone monitoring and providers as well, but will this actually be implementable in the real world, and will it actually work?

So I think the question that we're faced with today is there are clearly patients that are self selected, that are motivated, that will be monitoring their blood ketones for whom the benefit versus risk may be favorable, but for the population at large, I think we have to ask whether this will really be the case for many people who may not be as motivated to monitor their ketones and considering the specificity of the risk.

DR. BURMAN: Thank you. My personal comments sort of mirror what was said before, that it is a very difficult question, as I mentioned,

comparing the trial to the real world. But on the other hand, as was mentioned as well, the medications, the SGLT2 inhibitors, are already on the market and being used, I think we heard before in many patients. I forget the exact number; it might have been millions of patients. And there are no guidelines for those used that are supported by the FDA.

Is it better -- I raise just a theoretical question -- to have something on the market that is monitored and has a very strict REMS program, so that the patients who are on it, number one, have support with regard to getting the medication but also are monitored in terms of very select patients; and while maybe given less select patients, it would have a higher risk? Those are unanswerable questions. Everybody has to answer for themselves. But I do agree there is an unmet need.

Anybody have any further comments?

(No response.)

DR. BURMAN: Then let me try to summarize,

and this will be difficult and appreciate your comments as well. We were asked to assess the risk-benefit ratio. It seems to me that most of the panel thinks the risks probably are a little greater than the benefits, especially if it's translated to the real-world setting.

However, it's recognized that there is a need for such an agent, and further agents, in type 1 diabetes, and that the benefits probably are in A1c as we've talked about earlier, as well as blood pressure, both systolic and diastolic, although that is somewhat controversial.

Everyone agrees longer studies are needed, but it gets to the practical point, how long should the studies be, and how many patients in the meantime will be given the medication off label and have consequences, when maybe if it was under a stricter regimen and it was approved, it would be less. That's up for everyone to decide for themselves.

As my summary, please, all questions and comments appreciated. Dr. de Lemos?

DR. DE LEMOS: No --

DR. BRITTAIN: I think you made the comment that we thought that risk was greater than the benefit, and I don't think that's what I heard. I think what I have heard is there's just a lot of uncertainty about the risk versus the benefit.

DR. BURMAN: That's fair. Thank you.

DR. DE LEMOS: James de Lemos. I would just push back strongly against both points, about this concept of approving a drug so that we can monitor the use when we don't know that it's safe and effective seems like a incredibly slippery slope, and absolutely no would be my answer to that. Our role, and the agency's role, is to make sure that in the package that submitted, we have great evidence that the risk-benefit is favorable. If we don't have that, putting it on the market so that we can learn more about it in a regulated way does not seem like the right way to go.

DR. BURMAN: Thank you. I appreciate that. Of course, it was raised for our discussion.

Anybody else have any other comments?

(No response.)

DR. BURMAN: Then, thank you. From the FDA's standpoint, is there anything we haven't mentioned that you wanted to talk further about?

DR. YANOFF: I can't think of anything, Dr Burman.

DR. BURMAN: No problem. Thank you very much.

DR. YANOFF: You guys have been very thoughtful.

DR. BURMAN: Thank you.

Amazingly enough, we're a little bit ahead of time, so I think we do have time for a break. It's 3:30. We'll come back at 3:45 and address the final question and voting question.

(Whereupon, at 3:27 p.m., a recess was taken.)

DR. BURMAN: I'll call the meeting to order. Thank you.

We will now proceed with the voting question of the committee. I would like to remind public observers that while this meeting is open for

public observation, no comments will be recognized. We will 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 have entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or you wish to change your vote, you may 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. The DFO will 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. You can also state, and should also state, the reason why you voted as you did. We will continue in this same manner until all questions have been answered or discussed.

If there are no specific questions, we will read the question. Do the available data suggests

that the benefits outweigh the risks and support approval of empagliflozin 2.5 milligrams administered orally once a day, as an adjunct to insulin to improve glycemic control on adults with type 1 diabetes mellitus?

If yes, please explain your rationale and comment on whether any additional studies should be required after approval. If no, please describe what further data you believe the applicant should provide to establish a favorable benefit-risk profile to support approval.

Are we ready to vote? Any questions about the voting process?

(No response.)

DR. BURMAN: No? Then I think we should proceed with the vote. It keeps flashing.

(Voting.)

DR. BURMAN: Has everyone completed voting?

LCDR BONNER: For the record, 2 yes; 14 no; zero abstain.

DR. BURMAN: Thank you. Now that the vote is complete, we'll go around the table and have

everyone who voted state their name, their vote, and if you want to, you can state the reasons why you voted as you did into the record. Dr. Chrischilles??

DR. CHRISCHILLES: Yes. Elizabeth Chrischilles. I voted no, and my reason was predominantly related to lack of sufficient evidence around efficacy.

DR. YANOVSKI: Jack Yanovski. I voted no because I think the data, unfortunately, are not quite adequate to support evidence for safety or efficacy. I think the trial that needs to be done has been well described. There needs to be a sufficient number of participants for long enough; that a better estimate of both benefit and risk over at least a year needs to be determined. Additional outcomes that might help the likelihood of this medicine being found beneficial would include outcomes related to kidney health and perhaps other aspects of diabetic type 1 disorder.

I also think that there needs to be more study of the subgroups whom might best benefit to

determine whether there is a subgroup that could be approved with great alacrity for long-term therapy, and there also needs to be more investigation of how to build an adequate risk evaluation and mitigation strategy for medications like the SGLT2 inhibitors in general; in other words, how do we assure adequate testing with ketone monitoring, as well as for glycemia, in order to do our best to minimize the risks from such medications.

Lastly, in terms of the case definitions, we've had a lot of discussion about how specific the categories should or should not be when assessing safety, and I think we should accept the fact that these medications, as a class, are likely to have risk related to a generation of ketones, and therefore it would be best to be most inclusive and maybe even considering categories like aborted DKA, or illness addressed early on may be very important to know, and then discover how best to manage those using patient data.

DR. BURMAN: Thank you. Dr. Kalyani?

DR. KALYANI: Rita Kalyani. While there's

an acknowledged unmet need for people with type 1 diabetes to have new and innovative treatments, as we've heard about today, as an endocrinologist, I share that excitement and enthusiasm for new therapies for people with type 1 diabetes. The safety balanced with the benefit, primarily efficacy, for any new treatment for the broader population has to be concerned and not just those who are truly self-selected.

The evidence presented today, primarily EASE-3, which was one randomized control trial, raised uncertainty regarding the adjudication of ketoacidosis and the reliability of those categories. As we've already discussed, there were many more ketone-related events when the combined broader category was considered in empagliflozin 2.5 versus placebo. To me as a healthcare provider, I wonder what the clinical significance of this will be in real-world settings, where patients won't be as closely monitored or checking blood ketones probably as often.

The A1c reduction of 0.3 percent was

significant. There was uncertainty regarding the durability, and I think that there needs to be longer term studies to demonstrate greater certainty both for the benefit and also for the safety of this dose of empagliflozin.

DR. BURMAN: Thank you.

DR. NASON: My -- sorry.

DR. BURMAN: Excuse me. Dr. Nason?

DR. NASON: My name is Martha Nason. I voted no. The question says do the available data suggest that the benefits outweigh the risks, and I'd say yes to this, but suggest is not enough for approval. It's enough for optimism. It's enough for enthusiasm for the next study. I hope it will be enough that you will have an easy time enrolling in a further study, especially given the unmet need and the amount and danger of the off-label use. That seems like a crucial step.

As others have said, this just comes down, to me, to not enough largely safety data. The fact that all the confidence intervals for ketone events, or for even DKA, go up to a hazard ratio of

3 or 4, that's too high a risk, still, within the realm of possibility, to me. I think from a safety point of view, we need longer term data and more diversity.

Also, from an efficacy point of view, this would benefit that longer term study, durability, replication, and hopefully continuous glucose monitoring, even though I do think it looks like there was a significant effect on week 26 A1c.

One more quick point about the case definition that, as I've mentioned, we've talked about a lot. I agree that there should be a wide net cast for that, but one comment I want to make, because I don't think it's come up, is that it also does still need to have some sort of specific algorithm for how it's going to be defined because, as the sponsor pointed out, it is important that the case and the adjudication be blinded, but sometimes there can be things that can unblind in maybe other side effects of the drug or something like that.

So I would just want to see that even as the

case definition or the criteria for going to adjudication is broadened, it's still, as much as possible, clear, algorithmically, who's going to be considered a case or who's going to be sent for adjudication in order that no biases sneak in. There might be a suggestion that somebody's glucose was still lower, even though everything else went up, so maybe they could be on the drug, for instance. So that's just an aside that I don't think came up.

MS. McCOLLISTER-SLIPP: I voted yes.

DR. BURMAN: Please state your name.

MS. McCOLLISTER-SLIPP: Oh, I'm sorry.

DR. BURMAN: No problem.

MS. McCOLLISTER-SLIPP: Anna McCollister, consumer representative. I voted yes simply because I think that the data did suggest that the benefit was commensurate with other studies that we've seen in other classes. The study population was low, and I think that was unfortunate. And as a result, I'm not exactly heartbroken over the fact that the committee vote went the way that it did

because I think we do need to hold sponsors to a high standard for the data they submit.

Having said that, I do think we need to have these discussions with a very sober understanding of the real risks that are currently present amongst patients with the current therapies available. We live with risks. You hear all the time about patients dying; not because of this study drug or other study drugs, but because of the inadequacy of treatments. We need to press for more treatment options, and I think patients are willing to take a risk and mitigate against that risk if there is a clinical benefit that they find meaningful.

I do hope this gives the agency the ability to -- and as a patient, I would like to challenge the diabetes research community to do whatever it is we need to do to validate time in range, or come up with other measures that are validated, whatever that level of evidence needs to be. We have to do that. We've got so much evidence that A1c is inadequate for actually assessing benefit that's

meaningful to patients.

I also hope that this can be a challenge to the diabetes research community to do more work to understand diabetic ketoacidosis. This seems to be way understudied and very poorly understood.

MS. LELLOCK: Carling Lellock, patient representative. I voted no because while there is a risk, and as a patient, I'm willing to take risks, and I think a lot of us are, I would potentially like to see a bigger benefit, so if we could have a longer study to see if the benefit is longstanding. As well, as some of those other secondary endpoints that I think are more important to me as a patient, I do appreciate that there is that need. I need it as well. So that's the reason why I voted no. I think there needs to be some more to it.

DR. WEBER: Tom Weber. I clearly recognize the need for additional non-insulin --

DR. BURMAN: Dr. Weber, excuse me. Could you, for the record, say how you voted?

DR. WEBER: Oh, I'm sorry. Tom Weber. I

voted no. I just want to say I clearly recognize the unmet need for additional non-insulin, glucose-lowering therapies that limit the risk of hypoglycemia and actually may facilitate weight loss and improve blood pressure control. There's also a need to address and improve patient-related outcomes that are increasingly recognized as clinically important, such as time and target.

That said, I don't feel that the data presented today on empagliflozin 2.5 milligrams were acceptable from a risk-benefit profile to qualify for approval by the FDA. I do feel the data is very promising and would recommend a more robust assessment of efficacy and safety, specifically at least a two-year clinical trial adequately powered, and adequate to establish efficacy in hemoglobin A1c, and also gather adequate patient-year exposure to more definitively and acceptably characterize the risk of diabetic ketoacidosis.

DR. NEWMAN: Connie Newman. I voted no. I feel, as many here do, or probably all of us, that

there is an unmet need for additional safe and effective treatment for people with type 1 diabetes. However, the data available to us and the data that are available for empagliflozin 2.5 milligrams are not sufficient to adequately characterize the benefit and the risk.

More data are needed, and I believe that there should be at least one additional clinical randomized-controlled trial of at least one year duration, with a consideration to including microvascular outcomes and also a consideration to extending the trial beyond one year, perhaps in an open-label fashion so we can get more data about safety.

Also, I think it would be very helpful to revise the adjudication strategy so that it is more sensitive, and also it would be helpful to test the risk mitigation strategy in a clinical trial.

DR. EVERETT: Brandon Everett. I voted no. I think, as we've all discussed -- and I don't want to rehash our discussion from the past couple hours -- there's a substantial unmet medical need

here. So I think, compared to perhaps some other conditions, with respect to efficacy, there's a lower bar in terms of what we might accept.

In that regard, I think I'm willing to accept that a real hemoglobin A1c of 0.3 percent is of clinically meaningful benefit to patients with type 1 diabetes, but I don't feel like that has been adequately characterized with the small number of patients who were tested on the dose that's at issue today, the 2 and a half milligrams per day.

I think given that our recommendation is to do another study that is larger and of longer duration, that affords the opportunity to prespecify some secondary endpoints and to reserve alpha for those, including important ones such as weight reduction and blood pressure reduction, but also others that may be important to patients with diabetes, including episodes of hypoglycemia and also time in the therapeutic range. Those, of course, would have to be determined a priori probably with help from the agency.

With respect to what data I would need to

actually approve this, it would be more patient-years of exposure, both for the efficacy, as I mentioned, but, in particular, for the risks and for the risks of diabetic ketoacidosis. I think, in addition, strategies to mitigate that risk are appropriate and should be included as they have been today, but consideration of what that might mean, whether it's with your prescription, you get a point-of-care ketone monitoring device or something along those lines.

Finally, I think it's important to emphasize that we owe it to patients with type 1 diabetes to do this right and to provide sufficient evidence to know that we're offering them a benefit and to well characterize the risks.

I think doing a study with 240 patients on active therapy probably doesn't quite meet that bar in terms of respecting the breadth and severity of illness of the patient population that we're hoping to address with this therapy and that characterizes that patient population. So I think, out of respect for them, I voted no and feel that a

larger study of longer duration is appropriate.

DR. MUNIR: Kashif Munir. I voted yes, and I knew I was going to be in the significant minority on this. Like I said, I was kind torn both ways. I think at the end of the day, I agree, it would have been nice to see more data and a longer trial, but I feel like the data were what I expected them to be. I felt like the DKA risk would be there, it's real, but it would be less than the higher doses, and I felt like the efficacy would be less than the higher doses, and that's exactly what we saw.

So I didn't feel like this trial was a surprise. Even though it was one trial and maybe not as big as we wanted or as long as we wanted, I didn't feel like it was really anything unexpected or anything that I wouldn't have predicted to see. So I feel like, with that being said, there is definitely a role for these medications -- I've used them myself -- in people with type 1 diabetes. I feel like, really, using a lower dose, sacrificing some efficacy but really helping on the

safety end of things, is a wise way to go. Some of us do use existing medications and have people cut them as they're using them now as well.

So that was mainly the reason I felt like there was enough, even though it was borderline, but enough there to give it a yes vote.

DR. BURMAN: Ken Burman. I voted no. As always, it is a very difficult decision to balance the benefits and risks. My opinion as an endocrinologist is that the A1c decrement was mild or slight, but statistically significant and probably clinically significant, and borne out by other previous studies of drugs that are already approved with a small 0.3 or so percent, a decrease in A1c.

I think the effects beneficially on blood pressure, both systolic and possibly diastolic, were real, and the effects on weight were real as well. But on the other hand, as an endocrinologist, of course we are worried about the increased risk of diabetic ketoacidosis, as we've seen earlier with a mortality rate -- I think it

was quoted as something like 0.4 percent -- and a high morbidity rate as well.

I think there was an increased risk of diabetic ketoacidosis in this trial that probably would be magnified in the real world. Comparing the real world to the trial, of course, the patients were more compliant in the trial. They measured ketones more frequently. Many were on CGM, and they had education that was meticulous, that could be given in the real-world setting as well.

It then comes down to risk versus benefit, and to me it was a slight increased risk compared to the benefit. It's relevant, of course, to have a longer term study in a real-world setting, and the question is, could this be performed before approval or after approval?

I certainly understand it would emphasize the practical issues of having this study performed prior to approval in terms of time and how long it should be, and probably it should be for a year if we were going to do it with some of the outcomes

that were noted, and specifically more attention, if possible, to diabetes and kidney DKA. Thank you.

DR. PAI: Majunath Pai. I voted no, primarily because I felt like the effect was not durable in terms of benefit. I think a key feature for the study design was, again, the dose selection. This idea that dose equals exposure is not exactly correct. So I think the dose justification, which was based on urinary glucose excretion, how that translates to hemoglobin A1c or DKA risk is not really clear to me.

So this idea that one dose would fit all may not be true in this population, such that for a future trial design, if someone is at 2.5 milligrams, there may be a subpopulation that needs 5 milligrams or a population that needs less. So I think there needs to be a lot more work done to justify the dose. In terms of safety, I think, clearly, longer patient exposure and a larger study sample size is going to be very important to answer that question.

DR. LOW WANG: Cecilia Low Wang. I voted no. As an endocrinologist and diabetologist, a significant proportion of patients that I see, both in the clinic setting as well as in the hospital, have type 1 diabetes. So I was really excited when I saw the topic of today's meeting, that I might be able to recommend approval for a new drug for type 1 diabetes because there's such significant unmet need. But unfortunately, I do think that, of course, when the FDA approves a drug means that they feel it's safe and it's supported by significant and adequate safety data, and in this case, we haven't seen that.

So as others have said, I think we need a larger, longer randomized-controlled trial on the 2.5-milligram dose. I think we do have some evidence that that is the dose to go with, but I think we need to see demonstrated reproducibility and durability of the benefits both on A1c reduction and possibly other benefits as well, maybe decreased microvascular complications. We need to see more accumulated safety data.

I would love to see testing of the DKA risk mitigation strategies. We don't even know how often to test for ketones. And as mentioned before, I think we need to see a broader definition of the positively adjudicated DKA cases or ketosis cases. And lastly, I would also like to see some of this information about subgroup benefits fleshed out.

DR. DE LEMOS: James de Lemos. I also voted no. It was, actually, a fairly clear decision for me, not because I don't think the drug is potentially approvable in the future, but because I just don't have a sense of whether this class of agents is safe, even at low doses in this patient population. Giving a drug that can cause DKA to patients with type 1 diabetes makes me nervous intrinsically, and the database here is not adequate to ensure safety, and nor would a second trial of this size.

I think that the next study that needs to be done has to focus on safety with regard to DKA and has to be large enough to do that. It's highly

likely that the A1c findings will replicate; it's a continuous measure. I'd be very surprised if that doesn't, but we need a trial large enough to get a precise signal about DKA rates, and that trial might even include randomization to different risk mitigation strategies, including a higher and lower intensity one that would be more likely reflective of what happens when the drug rolls out into clinical practice.

I'd suggest that that trial would have to be at least several thousand individuals but would not need to randomize 1 to 1. You could have a strong excess of patients randomized to the low dose empagliflozin because the real question is the precision around the estimate of DKA in the treatment group and, really, a hard estimate of what that number might be so that individuals can decide whether this drug is approvable.

Without that, I don't think I will -- even if this came back with a second study, without adequate confidence that the DKA signal has not materially increased, I would not be comfortable

approving it.

DR. BRITTAIN: Erica Brittain. I voted no. I remain optimistic that the regimen will ultimately prove to be useful. There wasn't anything very worrisome about the results of the study, but just that a one 6-month study was insufficient to assess the trade-off between benefit and risk.

In terms of designing the next trial, it seems like someone has to decide what's an acceptable upper bound for the relative risk of DKA, given the benefit of 0.25 and the hemoglobin A1c. Someone has to make -- or not someone. Some group has to decide what that is, and then that will naturally be through a study design. I also agree it will help the ability to conduct this study to have a broader definition of DKA, so it's not such a rare event.

DR. BLAHA: Mike Blaha. I also voted no in this case. I struggle a lot with the perceived imbalance, in my view, of the outcomes here, of A1c on the efficacy side, which is a lab measure, but

certainly over the long term has benefit on microvascular, perhaps macrovascular, outcomes, and then a DKA, which has immediate effects on the patient that can be fatal. So balancing those is difficult, especially in light of a very small margin of efficacy.

Of course, like I said before, and everyone has said, in balancing those, it becomes much more complicated with the very limited safety database and with very poor precision, in my view, of the point estimate of risk of DKA.

I personally think that a low-dose SGLT2 inhibitor strategy is promising. I actually don't have a lot of questions about efficacy. I tend to agree that the A1c benefit will probably be sustained, although small, especially if low doses are used. So therefore, I'd encourage the sponsor to do another large study as was mentioned, but this should be a safety study. It's different than what's been presented to us so far.

The primary outcome here would be what's called broad DKA, and we have to think carefully

about what that means. But it would be a safety study like we're used to seeing and that we've required for other classes of drugs. We have to prove this is safe. That's the outstanding question; and certainly data on A1c, blood pressure, and weight loss would be good.

I would just say that I think this is really worth the investment. I guess from the company's point of view, I would certainly think that was worth the investment. But also for the biology and understanding this disease, it would be extremely worth the investment. I think it would teach us a lot about type 1 diabetes, DKA, as people have mentioned, and I think it would teach us a lot about SGLT2 inhibitors, but also just the concept of adding on therapies for insulin reduction in type 1 diabetes where there seems to be a large gap in knowledge.

So I think that would be extremely worthwhile to do. I think if one were to determine the safety margin that would be reasonable would be and what a DKA definition would be, the trial could

then be designed.

DR. BURMAN: Thank you. Before we adjourn, are there any further comments from the FDA?

DR. YANOFF: Well, I just want to thank the applicant for all their hard work on behalf of patients with type 1 one diabetes; and the committee for their thoughtful discussion; and the open public hearing speakers, their helpful comments.

Just to reiterate what I said this morning, we do recognize the unmet need, and FDA is dedicated to helping to facilitate the development of new therapies for patients with type 1 diabetes that are safe and effective. We are open to development of novel endpoints for diabetes that are important to patients beyond A1c, but more work needs to be done there. We look forward to continuing our work on behalf of all the stakeholders, so thank you very much.

Adjournment

DR. BURMAN: Thank you. I'd like to thank all of the members for their diligence and

appropriate comments; the sponsor for a very nice presentation; the FDA for their presentation as well; and of course the OPH members and speakers.

With that, let's adjourn the meeting.

(Whereupon, at 4:15 p.m., the meeting was adjourned.)