FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE MEETING

(EMDAC)

January 10, 2013

Location:

The Great Room

White Oak Conference Center

White Oakes Campus

10903 New Hampshire Avenue

Silver Spring, MD 20993

Reported by: Natalia Thomas

Capital Reporting Company

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P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. THOMAS: I'd first like to remind everyone present to please silence your cell phones, Blackberrys, and other devices, if you've not already done so. I'd also like to identify the FDA press contact, Ms. Morgan Liscinsky. If you're here, present, please stand.

Good morning. My name is Abraham Thomas. I'm the Acting Chair of Endocrinologic and Metabolic Drugs Advisory Committee. I will now call the meeting of the Endocrinologic and Metabolic Drugs Advisory Committee to order.

We will go around the room and please introduce yourself. We'll start with the FDA and Dr. Mary Parks to my left and go around the table.

DR. PARKS: Good morning. I'm Mary Parks. I'm the Director in the Division of Metabolism and Endocrinology Products.

DR. GUETTIER: My name is Jean-Marc Guettier. I'm a Diabetes Team Leader in the Division of Metabolism and Endocrinology Products.

DR. KWON: KC Kwon, the Clinical Reviewer in the Division of Metabolism and Endocrinology Products.

DR. SOUKUP: Mat Soukup, Team Lead, Division of Biometrics 7, Office of Biostatistics.

DR. HIATT: William Hiatt. I'm a Professor of Medicine at the University of Colorado, School of Medicine, Division of Cardiology.

DR. KNOWLER: Bill Knowler, Chief of the Diabetes Epidemiology and Clinical Research Section of the NIDDK in Phoenix, Arizona.

DR. GREGG: Ed Gregg, Chief of the Epidemiology and Statistics Branch at Diabetes Division in CDC in Atlanta.

DR. CAPUZZI: Yes, I'm David Capuzzi. I'm Professor of Medicine and Biochemistry at Thomas Jefferson University in Philadelphia, and also a member of the medical staff of the Lankenau Medical Center.

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

DR. BRIGGS: Caleb Briggs, Acting Designated Federal Officer, EMDAC.

DR. THOMAS: Abraham Thomas, Division Head, Endocrinology, Henry Ford Hospital, Detroit, Michigan.

DR. COOKE: David Cooke in Pediatric Endocrinology at the Johns Hopkins University School of Medicine.

MS. KILLION: Rebecca Killion. I'm the patient representative for the FDA.

DR. KAUL: Good morning, Sanjay Kaul. I'm a cardiologist at Cedars-Sinai in Los Angeles, Professor at UCLA School of Medicine.

DR. COOK: Good morning. Nakela Cook. I'm a cardiologist in the Division of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute, NIH.

DR. PROSCHAN: Hi, I'm Mike Proschan. I'm a Mathematical Statistician at the National Institute of Allergy and Infectious Diseases at NIH.

DR. SAVAGE: I'm Peter Savage. I'm an endocrinologist and senior advisor for clinical studies at the Division of Diabetes, Endocrinology, and Metabolism, NIDDK.

DR. MALARKEY: I'm David Malarkey. I'm a veterinary pathologist. I'm the Head of the Pathology

Group at the National Toxicology Program.

DR. LEWIS: I'm Julia Lewis. I'm a nephrologist, Vanderbilt, Professor of Medicine.

DR. PALEVSKY: Paul Palevsky. I'm Chief of the Renal Section at the VA Pittsburgh Healthcare System and Professor of Medicine at the University of Pittsburgh.

DR. RASMUSSEN: I'm Mads Rasmussen from Novo Nordisk. I'm the industry representative on the panel.

DR. THOMAS: 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 Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask that the advisory committee members take care

that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting, with the media, until its conclusion.

Also the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you. Conflict of Interest Statement

DR. BRIGGS: The Food and Drug Administration, FDA, is convening today's meeting of the Endocrinologic and Metabolic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, 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 USC, 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 USC, 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 particular individual's services outweighs his or her potential financial conflict of interest.

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 and children, and for purposes of 18 USC, Section 208, their employers.

These interests may include investments,

consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of the new drug application, NDA, 204042, canagliflozin tablets, proposed trade name, Invokana, submitted by Janssen Research and Development, LLC. Canagliflozin is a member of the sodium-glucose co-transporter 2, SGLT2, inhibitors, and was developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This is a particular matters meeting during which specific matters related to Janssen's Invokana, canagliflozin, will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee 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. Mads Frederik Rasmussen is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry.

Dr. Rasmussen's role at this meeting is to represent industry in general and not any particular company. Dr. Rasmussen is employed by Novo Nordisk.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms, not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. THOMAS: The Chair will now recognize Dr. Knowler who has a comment to state before the start of the meeting.

DR. KNOWLER: Yeah, I would just like to

state that I'm personal friends and a long-term collaborator with one of the presenters, Ed Horton, although we have not discussed this drug or this meeting prior. So I believe that does not affect my objectivity.

DR. THOMAS: Thank you. Before we continue, Dr. Rosebraugh, would you introduce yourself?

DR. ROSEBRAUGH: Curt Rosebraugh, Director, Office of Drug Evaluation II. Introduction/Background

DR. THOMAS: Thank you. We'll now proceed with the FDA opening remarks from Dr. Jean-Marc Guettier. I'd like to remind public observers at this meeting, that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

DR. GUETTIER: Good morning. My name is Jean-Marc Guettier and I am Diabetes Team Leader in the Division of Metabolism and Endocrinology Products. I want to start by welcoming all participants to this advisory committee meeting, and would like to take this opportunity to thank, in particular, Dr. Thomas for chairing the meeting, and the panel members for their

willingness to participate.

The advisory committee was convened to discuss the new drug application for canagliflozin. The applicant is seeking to indicate canagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The applicant is also proposing to limit the use of canagliflozin in patients with severe renal impairment and patients with end state renal disease. Canagliflozin is a new molecular entity and would introduce to the U.S. market a new class of antidiabetic agent.

Canagliflozin works by inhibiting the sodium glucose co-transporter 2, SGLT2, for short. Inhibition of this co-transporter in the proximal renal tubule decreases urinary glucose reabsorption and promotes urinary glucose excretion.

The glucose lowering effect of canagliflozin is thus a result of its glycosuric effect. Since glycosuria is dependent on both prevailing plasma glucose and renal function, it is expected that the glucose lowering benefit of canagliflozin will wane

with declining renal function.

The rise in urinary glucose concentration caused by SGLT2 inhibition also results in increased urinary water retention and promotes diuresis. SGLT2 inhibition therefore exerts both a glucose lowering effect and an osmotic diuretic effect.

This morning you will hear from the applicant, followed by the FDA, on topics related to the efficacy, safety, and tolerability of canagliflozin. After each of the final applicant and FDA presentations, the committee will have the opportunity to ask for clarifying questions.

At noon, we will break for lunch. We will reconvene at 1:00 p.m. for a one-hour open public hearing session. The rest of the afternoon is reserved to address the three discussion points and the two voting questions.

In the next few minutes, I will go over each of the discussion points to provide clarification. For the first discussion point, we are asking the committee to address the benefit risk profile of canagliflozin use in the population of patients with type 2 diabetes

and moderate renal impairment.

For this particular question, the moderate renal impairment population is defined as the population of patient with diabetes with an estimated GFR between 30 and 60 mLs per minute. This morning you will hear presentations detailing how renal function impacts canagliflozin's glucose lowering ability.

You will also hear presentations describing how canagliflozin use impacts renal function. An increased for genital mycotic infection is seen with canagliflozin. The last bullet is asking whether this risk and the consequence of this risk should be weighed any differently in this particular population of patients.

You should also feel free to discuss any additional points relevant to this general topic of discussion, which are not covered here or in the three following discussion points.

We are interested in your assessment of the risk benefit balance for this particular subpopulation of patients with diabetes, because the prevalence of chronic kidney disease in diabetes is high. According

to the 2005, 2010 National Health and Nutrition Survey, approximately 20 percent of patients with diabetes had chronic kidney disease defined by an estimated GFR below 60 mLs per minute.

In the second discussion point, we're asking the committee to weigh in on the bone fracture data seen in the canagliflozin program. The discussion should focus on the significance of this data to the overall risk benefit profile.

Bone metabolism data, mineral metabolism data, and bone density data will also be presented. We are interested in your interpretation of these data and whether you believe these data are clinically relevant and inform the risk of fractures.

In the third discussion point, we are asking you to comment on the meta-analysis of cardiovascular events across the Phase II and III programs. The bullet points refer to specific topics that will be covered in today's presentations.

After you have finished the discussion session, we will ask you to vote on the two following questions. Question 4 asks, "Based on the data

submitted and considering the points of discussion in question 3, do you have any concern regarding a conclusion that a risk margin of 1.8 has been excluded for canagliflozin?"

The question should not be interpreted as simply asking whether the upper bound of the 95 percent confidence interval around the hazard ratio derived from the analysis of cardiovascular safety is below 1.8.

For this question, we want you to weigh the totality of the evidence surrounding cardiovascular safety, including the issues raised in discussion point 3, and tell us whether you have concerns in concluding that a cardiovascular risk margin of 1.8 has truly been excluded for canagliflozin. In your answer, we would like you to explain why you are or why you are not concerned.

Question 5 asks, "Based on the information included in the briefing materials and presentations today, has the applicant provided sufficient efficacy and safety data to support marketing of canagliflozin for the treatment of type 2 diabetes?" In answering

this question, you should again weigh all the efficacy and safety data presented both in the background document and at today's meeting.

Based on your answer, we would like to hear your opinion about additional pre- or post-marketing studies you would recommend to address any of the safety issues addressed today, or not covered today, but addressed in the briefing document.

I want to conclude this introduction by once again extending my gratitude to all participants and panel members, and look forward to a productive advisory committee meeting. Thank you.

SPONSOR PRESENTATIONS

DR. THOMAS: Thank you. We'll now proceed with the sponsor presentations. I'd like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such

transparency at the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

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

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have 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. Introduction

JACQUELINE COELLN-HOUGH: Good morning. I'm Jacqueline Coelln-Hough, Senior Director of Regulatory Affairs at Janssen Research and Development. On behalf of Janssen, I'd like to thank the committee and the representatives of the Food and Drug Administration for the opportunity to present canagliflozin as a new

treatment option for patients with type 2 diabetes.

As you've already heard, canagliflozin is a member of a new class, sodium-glucose co-transporter 2 inhibitors, which have an insulin independent mechanism. The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The proposed dose and administration is 100 or 300 milligrams once daily with specific recommendations for patients who should start with the 100 milligram dose. These indication and dosing and administration recommendations or proposals are based on an extensive Phase III development program.

In fact, the largest type 2 diabetes mellitus program submitted to health authorities to date, with 10,301 subjects enrolled in the Phase III program. There was long duration of treatment with greater than 2,800 subjects treated with canagliflozin for a year and a half or more.

The studies evaluated canagliflozin at each step of the treatment paradigm -- monotherapy, dual therapy, triple therapy, and add-on to insulin. There

was significant experience in vulnerable populations accounting for greater than 50 percent of the Phase III program.

These included longstanding diabetes, age by elderly or older patients, renal impairment, and subjects with cardiovascular disease or at risk of cardiovascular disease. We believe the totality of the data from the briefing materials and the presentations today support that canagliflozin provides substantial glucose control with the added benefits of weight loss and blood pressure reduction; has a safety profile that is characterized across the full continuum of patients with type 2 diabetes; has adverse drug reactions that can be managed; and that both the 100 and the 300 milligram doses provide a valuable additional treatment option to address the unmet medical need.

This is our agenda today. Following my introduction, you'll hear about the medical landscape and the need for new therapies to treat type 2 diabetes. This will be followed by a review of the mechanism of action of canagliflozin, an overview of the Phase III program, as well as a presentation of the

efficacy data.

Following that will be a discussion and presentation of the safety and tolerability data, and our final presentation will be an overview of the benefit risk of canagliflozin. At the conclusion of our presentation, we'll be happy to address any questions the committee may have.

To assist us, we have external experts with us. They are listed on this slide, along with their expertise and their affiliation. We have compensated these external experts for their time today, away from their patients and their research.

I'd now like to introduce Dr. Ed Horton from the Joslin Diabetes Center in Boston, a Professor of Medicine at Harvard Medical School, and a past president of the American Diabetes Association. Medical Landscape & Unmet Need

EDWARD HORTON: Thank you very much, Jacqueline. Good morning, everyone. I would like to give you a brief overview of the current landscape of diabetes in the United States, particularly type 2 diabetes and the various therapeutic options that we

have for managing it.

I'd just like to start though with this map of the estimated prevalence of diabetes worldwide and the projections of the changes that we're going to observe by 2030. This is described by many people as a worldwide epidemic of diabetes, and of course 90 to 95 percent of this is people with type 2 diabetes.

But in 2011, it was estimated that there are a total of 366 million people worldwide with diabetes and this is projected to increase by more than 50 percent by 2030. If you look, you can see that the increases are quite striking in different sections of the world, but here in North America we're looking that by 2030 we will have over 50 million people with diabetes here.

Now the various factors for this increase are really changes in lifestyle and one of the driving factors is of course the development of obesity. And I put up these maps that show the prevalence of obesity in diabetes between 1994 and 2009, and you can see there's a parallel increase in obesity and diabetes worldwide, and this is one of the major driving forces

behind this increase.

This is being called a dual epidemic of obesity and diabetes, and the current statistics are that 65 percent of adult Americans are overweight, as defined by a body mass index of greater than 25, and 32 percent are obese as defined by a body mass index of greater than 30.

There are now an estimated 25.8 million people with diabetes in the United States. That represents 11.3 percent of the adult population. And even more frighteningly there are now estimated to be 79 million people with prediabetes, defined as impaired fasting glucose or impaired glucose tolerance.

And the lifetime risk of developing diabetes for people born in the year 2000, so that's the 12 to 13- year-old children, is now estimated to be 33 percent for men and 39 percent for women. There's a tremendous economic cost of this epidemic of diabetes.

Total direct and indirect costs of diabetes in the U.S. in 2007 were estimated to be $174 billion, with direct costs of $116 billion, and indirect costs due to disability and lost work and so forth, of $58

billion dollars.

Most of this cost is really managing long-term complications. Diabetes is the leading cause of blindness in adults; the leading cause of kidney failure; and of non-traumatic lower limb amputations. The risk of heart disease and stroke is two to four times greater in people with diabetes than in those without diabetes.

Now there are many studies that have demonstrated the impact of improving glucose control as measured by hemoglobin A1c levels to reduce microvascular complications of diabetes. And there is emerging evidence to suggest that improvement of glycemic control also can have an effect to reduce macrovascular disease as well.

I put up here the data from three studies: the Diabetes Control and Complications Trial which was in type 1 diabetes; the Kumamoto Study in Japan which was in type 2 diabetes using insulin therapy; and the United Kingdom Prospective Diabetes Study done in the U.K. using a variety of agents to improve glycemic control.

And you can see in all three of these studies there was very significant reduction in the development of microvascular complications of the disease. And in the original studies, there were none statistically significant reductions in macrovascular events as well, and in the long-term follow-up of both the Diabetes Control and Complications Trial and the UKPDS we now know that are so-called metabolic memory or carryover effects of this early intensive treatment.

I show this slide from the UKPDS which shows the relationship between hemoglobin A1c levels and microvascular disease shown in the green line and myocardial infarction shown in the orange line. And you can see that lowering A1c, at any range, has a significant reduction in microvascular disease.

And there is also a less robust improvement in macrovascular events, myocardial infarction as well. Now, we've learned from the UKPDS though that this is progressive disease and I'll come back to that in a moment. But I think the results of the Diabetes Control and Complications Trial and the UKPDS and other studies have really led the various organizations to

set targets for hemoglobin A1c in our population.

Currently, the American Diabetes Association goal is less than seven percent. The American Association of Clinical Endocrinologists and the American College of Endocrinology recommend less than 6.5 percent as an appropriate target for A1c, but both organizations recognize that the closer we can get to normal value, that is six percent without significant hypoglycemia or other limiting factors, is really what our target should be.

And I wanted to emphasize the hypoglycemia part of it, because that is often one of the major limiting factors to achieving these targets. Now, more recently we've also recognized the need for individualization of treatment approaches and goals.

Intensive management with tight glycemic control can have dramatic long-term events. However, we know that in an older population that already has complications and particularly has cardiovascular disease, such as in the ACCORD trial, that there may actually be not benefits and actually some increase in risk involved with being too aggressive in trying to

improve our glucose levels in this population.

So the key to this is the individualization of therapy. And one has to take into consideration, as a clinician, to really evaluate each patient as an individual and take into consideration their age, their life expectancy, the presence or absence of complications, other comorbidities such as cardiovascular disease.

And I'd also like to mention here, impaired renal function as a major co-morbidity or complication of the disease that really has to be taken into consideration when we choose the appropriate targets and therapeutic agents that were going to use. And I do want to kind of emphasize that hypoglycemia, from my point of view certainly and many clinicians, is one of the major, major limiting factors of getting people to appropriate goals.

Now the other thing I wanted to point out is that we're making some improvements in achieving these goals, but we have a long way to go. And I put up here data from the NHANES studies, 1999, 2000, all the way up through 2003 to 2004 data, and you can see the

number of people or percentage of people that have achieved a hemoglobin A1c of less than seven percent is now over 50 percent, but we're still only in the latest data, still under 60 percent of achieving the goals.

And then if you look at the various segments of our population, you can see that there are some of the segments of our population that are not even at 50 percent of their goal. Now, we've also recognized over the years that type 2 diabetes is truly a progressive disease.

And these are the data from the UKPDS study, which I think is the one that was one of the first studies to really teach us the progressive nature of the disease. In the UKPDS study newly diagnosed people with type 2 diabetes were first given a six-month program of diet, exercise, and weight loss and they were able to get their starting A1c levels down to about seven percent before they were randomized either to conventional therapy or to the available treatments at the time the study was started: sulfonylureas, insulin, and in a subgroup of overweight individuals, metformin.

But you can see that over time all of the groups lost progressively their control. And we learned from that that study that this was due primarily to a progressive loss of pancreatic beta-cell function. Now many other studies have actually shown this as well. Just mention the studies in the Pima Indians looking at the progression, development of diabetes is shown as a major factor there, has been a progressive loss of beta- cell function and inability to compensate for the insulin resistance.

So schematically, the way we are now looking at the progression of type 2 diabetes is that there is a balance between insulin resistance on the one hand, and the ability of the pancreatic beta-cell to secrete adequate insulin to compensate for the insulin resistance.

In the normal glucose tolerance phase, these are well-balanced. But as one moves from normal glucose metabolism to impaired glucose metabolism to frank diabetes, and then on over time, there is a progressive loss of beta-cell function.

So one of the major goals that we have now is

try to restore and preserve beta-cell function in our patients. Now during the last couple of decades, we have had the development of many different medications that we can use to target the specific pathophysiological abnormalities that we're dealing with and I've just -- I don't have time to go into all of these -- I've listed the various targets on this slide.

But I wanted to point out that the increased glucose reabsorption in the kidney is one target that we have not any medications that are approved to use in the U.S. All of the other targets, we have various medications and I've just listed them very quickly on this slide.

So we're looking at -- we have a number of medications. There are currently five classes of oral agents and two classes of subcutaneously administered agents that are recommended both by the American Diabetes Association and the European Association for the Study of Diabetes, but they have limits.

We have limited efficacy and durability in some of the classes. Hypoglycemia, I've mentioned, is

a major limiting factor in some of them. Weight gain is a prominent feature in some of the medications that we have, using, and we're trying -- this is a real dilemma for many clinicians because we're telling our patients to lose weight, at the same time giving them medications that stimulate weight gain.

We have gastrointestinal side effects and we have limitations in some of the medications, patients with congestive heart failure, patients with impaired renal function and fluid retention and so forth. So in conclusion, I think we still have a need for new agents and new options to appropriately manage our patients.

And I think this is really recognizing that diabetes is a rapidly advancing epidemic, and failure to adequately control hyperglycemia can have devastating consequences on affected individuals and on society. Currently available antihyperglycemic agents do have limitations, which I've mentioned, and many patients are not achieving or maintaining the hemoglobin A1c goal of less than seven percent.

So with that, I would -- I know that's a very quick overview. I'd be happy to answer questions

after, but now I'd like to call on Dr. Meininger to really discuss the mechanism of action of this new class of compounds, the SGLT2 inhibitors. So Gary? Mechanism of Action, Phase III Program Overview, and Efficacy

GARY MEININGER: Good morning. The mechanism of action of canagliflozin is unique among classes of antihyperglycemic agents in that it works at the level of the kidney, where no other antihyperglycemic class of agents works. And thus, could be broadly combinable with all other antihyperglycemic agents.

Shown in the figure on the right, we see that glucose is freely filtered at the level of the glomerulus and then traverses the proximal convoluted tubule of the nephron, and then is reabsorbed by both the SGLT2 and SGLT1 transporters. Under normal glycemic conditions, no glucose should appear in the urine.

The SGLT2 transporter is primarily expressed in the kidney and is responsible for the majority of renal glucose reabsorption. The SGLT1 transporter, on the other hand, is responsible for only a small portion

of renal glucose reabsorption and plays a more prominent role in intestinal glucose absorption.

Canagliflozin is a potent selected inhibitor of the SGLT2 transporter. As shown on the figure on the right, in the presence of canagliflozin, glucose reabsorption is inhibited at the SGLT2 transporter. Thus, glucose is delivered throughout the nephron and ends up in the urine. In patients with type 2 diabetes the amount of urinary glucose excretion is approximately 80 to 100 grams per day, thereby reducing plasma glucose.

Additional contributors to glucose control include the reduction in body weight owing to the loss of glucose in the urine and the caloric equivalents. In addition, improved beta-cell function is also seen with canagliflozin and contributes to the improvement in glucose control.

Importantly, the mechanism of action of canagliflozin is independent of the action of insulin. This is important as it means that canagliflozin could be used in a broad range of subjects including subjects with minimal to no insulin secretion.

Shown here is the relationship between plasma glucose and urinary glucose excretion. The SGLT2 and SGLT1 transporters continue to reabsorb glucose up until a threshold, defined as the renal threshold for glucose. In healthy subjects, this threshold is approximate 180 milligrams per deciliter. At plasma glucose levels above this threshold, glucose begins to appear in the urine and the rate at which it appears is consistent with the glomerular filtration rate.

In patients with type 2 diabetes, the renal threshold for glucose is increased to approximately 240 milligrams per deciliter. This is an important point because it means that in patients with type 2 diabetes, glucose continues to be reabsorbed at much higher levels and thus contributes to the hyperglycemia seen in type 2 diabetes.

Canagliflozin pharmacologically lowers the renal threshold for glucose to a maximal lowering of the renal threshold for glucose to approximately 70 to 90 milligrams per deciliter. This too is an important threshold as it is above the threshold typically associated with hypoglycemia, and thus would mean that

canagliflozin would have a low risk for hypoglycemia.

The half-life of canagliflozin is approximately 11 to 13 hours and supports once daily dosing. It is excreted both by the kidney and the biliary system. Glucuronidation is the major metabolic pathway with no active metabolites produced. Importantly, no clinical meaningful drug-drug interactions have been observed.

Shown on the right is pharmacodynamic profile looking at renal threshold for glucose over a 24-hour period. You can see that with both canagliflozin 100 and 300 milligrams, the renal threshold for glucose is lowered throughout the 24-hour period and is lowered maximally be the 300 milligram dose.

Because of this lowering of the renal threshold of glucose over the 24-hour period, plasma glucose is also improved over the 24-hour period, shown in this study in patients with type 2 diabetes. The lowering of plasma glucose is very quick, within hours of dosing and improvement is seen in both fasting and postprandial glucose levels.

As you heard earlier from Dr. Horton, type 2

diabetes is associated with impaired beta-cell function. Canagliflozin improves indices of beta-cell function. Shown here, in one of our Phase III studies at 26 weeks, an index on the left in the fasting state and on the right in the postprandial state, showing improvement in beta-cell function. These effects are believed to be secondary to improved glucose control, rather than a direct effect of SGLT2 inhibition.

To summarize the pharmacodynamic effects of canagliflozin, both doses, canagliflozin 100 and 300 milligrams increase urinary glucose excretion with additional urinary glucose excretions seen with the 300 milligram dose. Both doses lower the renal threshold for glucose, but the 300 milligram dose does so throughout the 24-hour period.

Both doses improve fasting and postprandial glucose with additional benefits of 300 milligrams owing to the increase in urinary glucose excretion. In addition, the 300 milligram dose delays intestinal glucose absorption and contributes to a lowering of postprandial glucose values. This is detailed in our briefing book.

Finally, improvements are seen in beta-cell function at both the canagliflozin 100 and 300 milligram dose. As you've already heard, the canagliflozin Phase III program was a very large Phase III program conducted in over 10,000 subjects. Efficacy was assessed in all studies and was shown consistently on all efficacy parameters seen.

The Phase III program consisted of nine studies, some of which also had substudies. Six of these studies were dedicated placebo-controlled studies with primary endpoints between 18 and 26 weeks in duration. They study the broad use of canagliflozin from monotherapy all the way to add-on to insulin therapy.

In addition, we have two active comparator studies, both with primary endpoints at 52 weeks. The first was an add-on to metformin study examining canagliflozin 100 and 300 milligrams compared to a titrated dose of the sulfonylurea, glimepiride. The second active control study was an add-on to metformin and sulfonylurea in which we compared our top dose, canagliflozin 300 milligrams to sitagliptin.

In addition to these studies, we conducted several special population studies: a study in older subjects; a study in patients with renal impairment with baseline eGFRs between 30 and 50; and a cardiovascular study in over 4,300 subjects. This study is also termed CANVAS. The Phase III program was conducted worldwide with approximately a third of subjects coming from North America, the majority of which were contributed from the United States.

Baseline characteristics both worldwide and in the U.S. were very similar with one notable exception. That is, of the over 450 black or African-American subjects recruited in the program, the majority came from the United States and represent 14 percent of the U.S.

population recruited in this study, consistent with the proportion of blacks or African-Americans in the United States with type 2 diabetes.

In addition, a large proportion of patients who were of Hispanic or Latino ethnicity were recruited both worldwide and in the U.S. I will now review the results from our placebo-controlled studies, followed

by a review of the active-controlled studies and then discuss the efficacy in patients with renal impairment or Stage 3 chronic kidney disease.

I will conclude with some comments on hemoglobin A1c subgroup analyses. The primary endpoint in our placebo-controlled studies, as well as our active control studies, was that of the hemoglobin A1c. Additional efficacy parameters examined were body weight and systolic blood pressure. The primary efficacy population was that of the modified intention to treat population or mITT, which represents all randomized subjects who received at least one dose of double-blind study therapy.

The primary imputation technique was that of last observation carried forward. Additional sensitivity analyses were conducted and support the primary imputation technique. Shown here are the placebo- subtracted A1c changes from baseline.

As you can see, in a population of subjects with a generally mild to moderate hyperglycemia, as reflected by a baseline A1c around eight percent, we can see that canagliflozin 100 milligrams and

canagliflozin 300 milligrams provided consistent lowering on A1c.

The canagliflozin 100 milligram dose provided a placebo-subtracted lowering of approximately 0.6 to 0.75 percent. Canagliflozin 300 milligram dose provided additional A1c lowering and the A1c range between 0.7 and 0.9 percent. I first call your attention to the monotherapy study where we saw larger placebo-subtracted changes.

With the canagliflozin 100 milligram dose and the canagliflozin 300 milligram dose, a placebo-subtracted change of 0.9 and nearly 1.2 percent. I also call your attention to the add-on to insulin substudy. This insulin substudy was conducted within our large cardiovascular safety study.

It consisted of subjects who had a mean age of around 63 years and had a long duration of diabetes of over 16 years. The mean baseline insulin dose was over 80. These patients represent really end-stage treatment in type 2 diabetes. These are the subjects that have diminished beta-cell function, and yet canagliflozin lowered A1c in these subjects.

Because of the lowering in A1c, many more subjects on canagliflozin achieved an A1c goal of less than seven percent. And in many of our studies, relative to placebo, two to three times as many subjects achieved this goal. These are the same patients that Dr. Horton described earlier, who were not previously meeting their A1c goal.

In addition to lowering in A1c, body weight was also improved. The canagliflozin 100 milligram dose provided placebo-subtracted approximately a two percent lowering on body weight. And the canagliflozin 300 milligram dose provided additional body weight lowering, approximately three percent placebo-subtracted.

Because of the weight reduction seen with canagliflozin, many more subjects on canagliflozin achieved weight reductions of greater than or equal to five percent. Systolic blood pressure was also improved and was seen placebo-subtracted across the entire program, approximately three to five millimeters of mercury. Importantly, no clinically meaningful changes in pulse rate were seen.

Results from our active-controlled studies extend the data from our placebo-controlled studies. These studies had primary endpoints at 52 weeks and provide additional information on the sustainability of the effects on A1c, body weight, and systolic blood pressure.

Of course, because these are active-controlled studies, they also provide relative efficacy against two commonly used medications: glimepiride and sitagliptin. In our add-on to metformin study in which we compared canagliflozin 100 and 300 milligrams to a titrated dose of glimepiride in a population with a mean baseline A1c of approximately 7.8 percent, we can see that all three doses had rapid A1c lowering.

The glimepiride arm, shown in green, achieved an A1c nadir at approximately 18 weeks with an attenuation of the effect over the remaining 52-week period, consistent with that seen with other sulfonylureas. In contrast, canagliflozin 100 and 300 milligram doses achieved a nadir at approximately 26 weeks with a generally stable profile over the remaining 52-week period.

The primary testing strategy in this study was that of non-inferiority, with a prespecified non-inferiority margin of 0.3 percent. Because the difference between each dose of canagliflozin and the control was less -- showed an upper bound of the 95 percent confidence interval of less than 0.3, both doses were claimed to be non-inferior to glimepiride.

In addition, in a pre-specified step-down procedure, we also assessed whether or not the doses would superior to glimepiride. This was done was assessing the upper bound of the confidence interval because less than zero. As you can see, canagliflozin 300 milligram dose had an upper bound of the confidence interval less than zero, and thus statistical superiority was claimed.

Shown here is the body weight profile in the same study. Glimepiride had a characteristic increase in body weight, whereas canagliflozin 100 and 300 mg doses had a weight loss, achieving a nadir at approximately 36 weeks with approximately a stable profile through the remaining 52-week period.

Relative to glimepiride, canagliflozin 100

and 300 milligram doses provide a lowering in body weight of approximately 5.2 and 5.7 percent respectively which translates roughly to about nine to ten pounds. Shown on the left is the same diagram I showed on the prior slide. Within the same study and as shown on the right, we conducted a subgroup analysis of patients who underwent body composition analysis using the DEXA scanning.

The purpose of this DEXA scanning was to assess the proportion of weight loss attributable to fat mass or lean mass loss. As you can see, approximately two-thirds of the weight loss was attributable to fat mass loss, which is consistent with the proportion of patients who have weight loss seen with other modalities, including diet and exercise and other antihyperglycemic agents associated with weight loss. We also saw improvements in blood pressure relative to glimepiride.

In our second active-controlled study in which we compared canagliflozin 300 milligrams to sitagliptin on a background of metformin and sulfonylurea, we see that both treatment arms lowered

A1c relatively rapidly, achieving a nadir at approximately week 12. The sitagliptin arm had an attenuation of the effect over the remaining 52-week period.

In contrast, canagliflozin 300 milligrams achieved a relatively stable profile over the remaining 52-week period. At the end of the 52-week period, the difference between the two treatment arms was that canagliflozin lowered A1c relative to sitagliptin by approximately 0.37 percent on A1c. The primary testing strategy in this study was the same as in the prior active-controlled study in which we first tested for non- inferiority with a prespecified margin of 0.3 percent, and then tested for statistical superiority with an upper bound of zero for the 95 percent confidence interval.

Since the upper bound of the 95 percent confidence interval is well below zero, we claimed both non-inferiority and subsequently superiority to sitagliptin. In terms of body weight profile, sitagliptin had a characteristic weight neutral profile over the 52-week period. In contrast, canagliflozin

led to weight loss, achieving a nadir between 26 and 34 weeks.

At the end of the 52-week period, the difference in body weight was approximately 2.8 percent in favor of canagliflozin, which roughly translates to about a five- pound difference. Canagliflozin also improved blood pressure relative to sitagliptin.

Since subjects with moderate renal impairment have a reduction in glomerular filtration rate, the amount of urinary glucose excretion that would be expected in these subjects is reduced. As a result, the amount of urinary glucose excretion that can occur in the presence of canagliflozin is also reduced.

Nevertheless, important improvements in A1c, body weight, and systolic blood pressure were seen in these subjects. Shown here is our dedicated study in patients with moderate renal impairment who had a baseline eGFR between 30 and 50; so a bit more restricted than the full range of Stage 3 kidney disease.

These patients had a baseline mean A1c of approximately eight percent. Placebo-subtracted, the

canagliflozin 100 and 300 milligram dose provided approximately a 0.3 and 0.4 percent lowering on A1c. Because our program had three other studies which allowed patients to be randomized if their baseline eGFR was less than 60, we prespecified a pooling of these subjects to understand the full range of Stage 3 kidney disease of 30 to less than 60.

This population of renal impaired patients also was rather large, consisting of over a thousand subjects, so provided additional information on this important population. With a similar baseline mean A1c of 8.1 percent, we can see that canagliflozin 100 and 300 milligrams lowered A1c from baseline by approximately 0.5 and 0.6 percent.

Placebo-subtracted this translates to roughly about a 0.4 to 0.5 percent lowering on A1c for canagliflozin 100 and 300 milligram respectively. Because of the lowering in A1c, more subjects in both the study and the pooled renal population achieved the important A1c goal of less than seven percent.

Body weight loss was also seen with canagliflozin 100 and 300 providing approximately a 1.6

and 1.9 percent lowering on body weight relative to placebo. Improvement in systolic blood pressure was also seen.

We also conducted hemoglobin A1c subgroup analyses to determine if there was an interaction between a variety of subgroup factors and changes from baseline in A1c. As shown on this slide with placebo-subtracted differences with canagliflozin 100 milligrams on the left, and placebo-subtracted differences with canagliflozin 300 milligrams on the right, we can see that across a number of factors there was no interaction, including factors such as age, gender, race, ethnicity, geographic region, and BMI.

To subgroup factors had expected interactions. The first, baseline A1c. As seen with other antihyperglycemic agents, the higher the baseline A1c, the greater the lowering in A1c. Similarly, given the mechanism of action of canagliflozin, patients with higher baseline eGFRs also had greater lowering on A1c.

So in summary, on the primary efficacy endpoint of hemoglobin A1c, we saw consistent improvements across all Phase III studies, with more

subjects achieving the important A1c goal of less than seven percent.

We show sustained responses over 52 weeks on A1c, and meaningful, albeit lesser, reductions in A1c in subjects with renal impairment. Other efficacy parameters that I presented, including body weight and systolic blood pressure, showed consistent improvements over the 52-week period.

Finally, additional efficacy was seen with canagliflozin 300 milligrams relative to the 100 milligram dose. At this time, I would like to invite Dr. Peter Stein, Head of Development of Janssen R&D to provide an overview of the safety and tolerability of canagliflozin. Safety and Tolerability

DR. STEIN: Good morning. In our assessment of safety and tolerability we focused on pooled datasets, and so I'll begin my comments by describing the datasets that we created. I'll then review some of the adverse drug reactions and then provide some of the additional safety assessments that we performed.

You've seen this slide before. It just reflects the breadth of our Phase III development

program for canagliflozin; nine Phase III studies across the spectrum of type 2 diabetes treatment from monotherapy to combinations with insulin.

We did studies on background of specific diabetes treatments, as well as three studies in special populations, the study on older subjects focusing on bone safety and body composition, a study in patients with renal impairment and the CV safety studied, the CANVAS trial, done in subjects with or at high-risk for cardiovascular disease.

Now four of these studies had common design, common enrolment criteria, differing only by the background diabetes treatment, enrolled a general type 2 diabetes population, not selected for specific baseline characteristics. These studies were all placebo- controlled, 26 weeks in duration and so provided important pooled dataset. I'll refer to this as the placebo-controlled studies dataset, and I think in the FDA briefing book it's also referred to as Dataset 1 or DS1.

The next dataset we created we referred to as

the broad dataset and it's also referred to as Dataset 3 or DS3. This included eight of nine of the Phase III studies, all of the studies that included both doses of canagliflozin. This was large dataset including over 9,400 subjects.

To provide a comparison group with a comparable duration of exposure, we've pooled the placebo and active comparator groups together and I'll refer to this as the non-canagliflozin control group. Now turning to the baseline characteristics of these pooled datasets, let me focus first on the placebo-controlled studies dataset.

This reflects I think a fairly typical Phase III diabetes study population and a similar proportion of males and females mean age in the mid-50s. As you can see, a duration of diabetes of a bit longer than seven years reflecting the inclusion of both monotherapy and add-on to dual therapy studies. About 20 percent of these patients at baseline already had microvascular complications.

Before I turn to talking about the broad dataset, I want to say a few words about the baseline

characteristics in our CANVAS CV safety study, because this contributed more than 40 percent of patients into the broad dataset.

As you can see here, there was a male predominance in this study. The mean duration of diabetes was quite long; more than 13 years in these subjects. As you can see, almost half of these subjects already had microvascular complications at baseline. Of course, many had macrovascular complications.

The broad dataset pooling the general populations in the placebo-controlled studies dataset set and several other trials, and the more vulnerable populations in the CANVAS trial, as well as in the special population studies in renal impairment in the study in older diabetics provided the broad dataset.

As you can see, still a modest male predominance, a slightly older mean age relative to the placebo-controlled dataset, and as you can see, also a longer duration of diabetes at baseline with about a third of these patients with microvascular, many with macrovascular complications at baseline.

The exposure in the placebo-controlled studies study dataset, a bit shorter than the 26 weeks. Now for the broad dataset, we conducted three sequential analysis. Two of these analysis were included in the NDA; the last analysis provided in the four-month safety update. As you can see, the mean exposure was slightly greater in the canagliflozin groups relative to the non- canagliflozin group.

As you can also see, a predominance of these patients had already had nearly a year of exposure or more. Because this is the dataset with the longest exposure and our larger dataset, a lot of my comments with regard to the safety assessment will be from this dataset analysis.

Now turning to the summary of adverse events, as you can see, there was a slight increase in adverse events in the canagliflozin groups relative to the non-canagliflozin control group. There was a modest increase in adverse events leading to discontinuation. This was largely due to the adverse drug reactions which I'll say more about in a few minutes.

These individually and frequently led to

discontinuation, but cumulatively led to the modest increase in the discontinuation rate you see. Notably, serious adverse events, serious adverse events leading to discontinuation, and deaths were not imbalanced across the treatment groups.

Now turning to the adverse drug reactions, here shown are the adverse drug reactions which were identified in the placebo-controlled studies dataset. I'd like to just focus on a few of these; first, thirst, polyuria and pollakiuria. These likely reflect the effects of the osmotic diuresis from the glycosuria with canagliflozin treatment. Now these were generally mild to moderate in intensity and infrequently led to discontinuation.

Urinary tract infection was slightly increased with canagliflozin. I'll come back to talking about that more in just a minute. Male and female genital mycotic infections were also increased, and as you can see, the incidence of these was similar in the 100 and 300 milligram group and clearly greater than seen in the placebo group.

These were generally assessed as mild to

moderate in intensity, infrequently led to discontinuation, and generally responded to standard antifungal therapies, either oral or topical.

Now we also examined the broad dataset to look to see if there were additional adverse drug reactions that we could identify. And in this dataset we noticed an increase in the incidence of reduced intravascular volume related to adverse events.

Adverse events such as postural dizziness, orthostatic hypotension, hypotension and the like, and I'll say more about this is just a few moments. We saw infrequent adverse event reports of rash and urticaria imbalanced with a slight predominance in the canagliflozin groups with no reports of Stevens-Johnson syndrome or anaphylaxis.

In the individual Phase III studies we did see hypoglycemia in a dose-related increase in studies of the background of agents themselves associated with hypoglycemia, insulin, and sulfonylurea agents. In studies on the background of diabetes treatments not associated with hypoglycemia, diet, metformin, we saw a very low incidence of hypoglycemia with canagliflozin.

Now turning to some of the adverse drug reactions that I mentioned, starting with urinary tract infections here, an overview of urinary tract infections in our broad dataset population, you can see the incidence in this population of any urinary tract infection adverse event was slightly increased with canagliflozin, similar at the two doses.

Upper urinary tract infection adverse events were slightly increased with the canagliflozin 100 milligram group and not notably different with the canagliflozin 300 milligram group relative to the non-canagliflozin control group with a similar pattern for adverse events leading to discontinuation. Notably serious adverse events of urinary tract infections were not imbalanced across the treatment groups.

Now turning to the reduced intravascular volume related adverse events, because I noted we saw a dose- related increase in these adverse events in the more vulnerable population in the broad dataset. Importantly, adverse events leading to discontinuation and serious adverse events were not imbalanced across the treatment groups.

The terms that particularly were important in increasing the dose-related occurrence of these adverse events were dizziness, postural hypotension, and orthostatic hypotension. Now the Kaplan-Meier for the time to onset of these events I think is of note. As you can see, these increased over the first 12 to 18 weeks and after 26 weeks the increment in these adverse events with canagliflozin was not notably different than the increment occurring in the non-canagliflozin control group.

We looked to see if we could determine risk factors for these adverse events. We noted three risk factors that led to a more prominent dose-related increase: eGFR less than 60, so the Stage 3 CKD population; age greater than or equal to 75 years; and the use of loop diuretics. I would note that even in individuals with one of these risk factors, the events still were generally referred to as mild to moderate intensity by the investigators.

There was not an excess of adverse events leading to discontinuation or of serious adverse events. Now on the bottom row, I've provided the

incidence of these adverse events, individuals who have none of these three risk factors, and you can still see that there is dose-related increase, but much more modest than in individuals with one of these risk factors.

To summarize the reduced intravascular volume- related adverse events, as I noted these were dose- related, there was no increase in adverse events leading to discontinuation or serious adverse events. They were generally mild to moderate in intensity in a generally short duration. They were manageable often with adjustment in the patient's concomitant blood pressure lowering medications.

Risk factors I've identified as eGFR less than 60, age greater than or equal to 75 years, or the use of loop diuretics. And this is the method by which we identified the dosing recommendations to initiate therapy using the 100 milligram dose in individuals with any one of these three risk factors.

Now I'd like to turn to talking about some additional safety assessments that we've conducted. I'll start with CV safety. I'd like to start by

talking about the changes in LDL cholesterol and then share with you the results of a CV event analysis that we've performed.

As you can see, we saw a 4.4 milligram per deciliter and 8.2 milligram deciliter increase in LDL cholesterol; this data from our placebo-controlled studies dataset with 100 and 300 milligrams of canagliflozin. There were smaller increases in non-HDL cholesterol, small increases in HDL cholesterol with no change in the ratio, and a reduction in triglyceride.

To further assess the changes in LDL cholesterol, we also measured Apo B and NMR measured LDL particle number in archived specimens from one of our large Phase III trials. The increases were roughly about half as large as the increases we saw in the LDL cholesterol. Our assessment is that the increase in LDL cholesterol likely reflects the downstream consequences of the glycosuria induced by canagliflozin treatment.

I've summarized here the changes in the CV risk factors we've seen with canagliflozin. There were changes in two validated surrogate predictors of CV

risk:

the increase in LDL cholesterol, and the decrease that we've discussed previously in systolic and diastolic blood pressure.

There were also changes in a range of other CV risk factors; none validated as surrogate markers of CV risk. We think that the best way to understand the net impact of these diverse changes is to examine the outcome study results and I'd like to review those with you.

Now first, to just provide the background methodology, we predefined the composite endpoint of MACE-plus, CV death, non-fatal MI, non-fatal stroke, and hospitalized unstable angina. We conducted a stepwise CV meta-analysis pre-specified based upon the FDA diabetes CV guidance. Our first step, the current step that we'll provide the results from, was intended to meet the upper bound of less than 1.8 and had been planned when we reached 200 events within the composite.

Our step two would be planned to beat the upper bound of less than 1.3, and will be done when

have 500 events within the composite. So our step one meta- analysis included 201 events from all of our Phase II and III studies that were completed prior to February of 2012. There were more events in our CANVAS CV Safety Study, than in the non-CANVAS other studies in this CV Phase II, III meta-analysis population.

The results are shown here. The overall hazard ratio was 0.91 with the upper bound of 1.22. We did note that there was some differences in the hazard ratio estimate in the CANVAS study, relative to the non-CANVAS studies: 1.0 in CANVAS, 0.65 in the non-CANVAS studies.

Now in this slide I'm showing the hazard ratios for each of the individual types of events within the composite. As you can see, on the top row the composite of 0.91. The hazard ratios for the individual types of events, CV death, fatal and non-fatal MI, and unstable angina were less than 1.0, and the hazard ratio for fatal or non-fatal stroke above 1.0. But as you can see, the 95 percent confidence intervals around these estimates included 1.0, indicating that these differences would not be

statistically significant.

I'd also comment that the 95 percent confidence intervals also included the composite hazard ratio estimate of 0.91, suggesting that none of these individual type of events hazard ratio estimates would be meaningfully different from the composite.

Now in the background briefing book from the FDA, there were several issues that were identified and I'd like to discuss those a little bit further, including the early imbalance seen in the CANVAS trial and the differences in hazard ratio by the type of events.

First, the issue of the imbalance that was seen in first 30 days within CANVAS. In that trial, we noted 13 events in the MACE-plus composite in the canagliflozin groups, compared to one event in the placebo group, and I'd remind you there was a 2:1 randomization in this trial.

The Kaplan-Meier focused on the early time period as shown on the left. I think there's a number of points that are important to consider. The imbalance was not seen in an overall CV event analysis

population; the prespecified population where we had 15 events in the canagliflozin groups and five events in the placebo group with an overall 2:1 randomization.

As I'll show you in a moment, we saw considerable month-to-month variability in the frequency of events, and I'd also comment that the low rate that we saw in the placebo group is not typical of other CV diabetes outcome trials. We looked to see whether there was an association of these events with volume depletion or volume depletion related adverse events and I'll discuss that in just a moment.

We also looked to see whether the subjects with these early events were a more susceptible population, but in our review of this we noted their baseline characteristics differed not at all from the baseline characteristics in the overall CV meta-analysis population or in the CANVAS study itself.

Now here I'm showing the month-to-month hazard rate variability in the CANVAS trial; in grey, the placebo group, and in purple, the combined canagliflozin groups. As you can see, particularly over the first three months there was marked

variability. The low rate in the placebo group is seen here with the greater rate in the canagliflozin group.

But as you note, in the second and third month, the rate in the placebo group was actually higher than seen in the canagliflozin group in the first month, suggesting that this reflects marked variability rather than the meaningful difference seen in first 30 days.

But we went further to see if there was plausibility of the association of these MACE-plus events, could they be precipitated because of the volume depletion or dehydration? I think there's several points worthy of making in that regard. As I noted before, the volume-related adverse events increased linearly over the first 90 and even 120 days. On the other hand, the MACE- plus events were higher in the first 30 days, but the subsequent 60 days were actually higher in the placebo group.

The volume-related adverse events, as I previously discussed, were notably dose-related, more common in the 300 milligram group than in the 100 milligram group. On the other hand, the MACE-plus

events occurred with relative balance: seven in the 100 milligram group, and six in the 300 milligram group.

We didn't see crossover of any reports of reduced intravascular volume-related adverse events in subjects with MACE-plus events, and in reviewing their narratives, we didn't see descriptors suggesting consistency, consist reports of these type of adverse events or other signs or symptoms of dehydration or volume depletion.

Our conclusion from this review was that was no evident relationship of these MACE-plus events to the reduced intravascular related adverse events or dehydration, and that the early imbalance likely reflect the marked month-to-month variability that I've shown.

Now turning to the hazard ratio around the individual types of events, I commented earlier that all of these hazard ratio 95 percent confidence intervals included 1.0, but the fatal and non-fatal stroke hazard ratio estimate was above one.

Further assessment of this -- I'd like to

comment on several points. First, that the prespecified composite likely would provide the most robust assessment. We would expect more variability within the individual events, types with the smaller event number. We went further to look to see the plausibility of the association with canagliflozin treatment, whether this could induce dehydration, hypercoagulability, and therefore lead to the difference in stroke event rates.

First, I'd note that we saw minimal overlap in patients with stroke events having volume-related adverse events. We didn't (ph) note differences in their change from baseline and blood pressure or their increase in hemoglobin that was different from other patients who did not have a stroke in the overall program.

I'd also comment on the different time course for strokes relative to the volume-related adverse events. As I showed before, the volume-related adverse events occurred early, with most of these occurring within the first 18 weeks. On the other hand, the Kaplan-Meier for stroke separates after 18 weeks. I'd

also note the lack of dose relationship.

As I pointed out before, the volume-related adverse events were notably dose-related, where stroke events occurred with a similar occurrence in the 100 milligram and 300 milligram group. We examined whether there are differences in other events in the stroke continuum. Hence, we looked at the hazard ratio for transient ischemic attacks which did not reflect an imbalance.

We also looked to see whether there was other evidence of hypercoagulability. We looked to see whether there was a difference in the incidence of venous thromboembolic phenomenon, and I note that this was generally balanced across the treatment groups. I also noted that we didn't see an increase in the hazard ratio for MI or unstable angina. In fact, these hazard ratios were less than one.

And finally, I would point out that there is not a suggestion that there is an increase in the occurrence of strokes with diuretics. Our assessment is that this imbalance in strokes likely reflects a chance difference, although certainly further

assessment of this over time is appropriate.

So turning to the renal safety evaluation, I'll comment on changes from baseline in the estimated glomerular filtration rate and then talk about results for the urinary albumin to creatinine ratio. Shown here are the changes from baseline in our placebo-controlled study dataset for eGFR. This is a typical pattern that we've seen across our studies in our program; an initial reduction in eGFR, followed by a rise back towards but not to baseline.

We also provided a last observation carried forward analysis to assure that early discontinuation did not lead to the observed attenuation of the difference from the placebo group. And as you can see, the conclusions from that analysis would not be different from that of the last observation carried forward analysis.

I'd also comment, although I won't be providing the data, that the additional analysis we conducted was to look to see whether patients with outliers were different across the treatment groups, and what we saw was reflected by this pattern.

That is to say that if you look at the any time analysis of greater than 30 percent reduction from baseline, it's increased in the canagliflozin groups. But if you look at the last on-study drug value for the outliers, they are relatively similar across the treatment groups.

Now I'd also like to provide longer term data for changes from baseline in the estimated glomerular filtration rate. Shown on top is our comparator study to glimepiride on the background of metformin. And again, you can see over the 52 weeks a generally similar pattern that I described in the 26-week duration of the placebo- controlled studies; the initial reduction followed by a general move back towards but not to baseline relative to the changes seen in the comparator group.

On the bottom is our comparison study to sitagliptin on the background of metformin and a sulfonylurea. And again, a similar pattern with the canagliflozin treatment group; the initial reduction likely reflecting the hemodynamic effect of the drug reducing plasma volume, and then general stability or

attenuation back towards baseline for eGFR.

Now turning to the changes from baseline and eGFR in our patients with renal impairment, this, the dedicated 3004 study in patients with Stage 3 CKD with an eGFR baseline of 30 to 50. A similar pattern is seen with the initial reduction here. A greater percent an absolute reduction than seen in the placebo-controlled studies dataset with an attenuation back towards baseline, but certainly not to baseline with a difference at the end of 26 weeks of about two to three mLs per minute.

In our CANVAS trial, patients came back for follow-up visits and chemistry was obtained at those follow-up visits. And here I've looked at patients who've discontinued from that trial where we had chemistry values available. In the middle panel is the last on-study drug value looking at the eGFR mean percent change, and you can see the pattern that I've discussed before with the reductions in eGFR seen.

In the follow-up visits, you can see that the values were similar to those seen with the placebo group with the values rising back towards baseline.

And we also looked at the urinary albumin to creatinine ratio.

This was conducted in four of our Phase III trials: this, the largest dataset of urinary albumin to creatinine ratio from our CANVAS trial, the CV safety study.

I've divided this by baseline albuminuria. Patients with normal albuminuria in the top left. Patients starting with microalbuminuria in the bottom left, and then subjects with macroalbuminuria in the bottom right. As you can see, in patients with normal albuminuria there was minimal change in the albumin to creatinine ratio, not different from the placebo group.

In subjects with micro and macroalbuminuria, however, there was notable reduction in the urinary albumin to creatinine ratio. We also at the categorical progression -- patients who progressed more than one stage of albuminuria from normal to micro or macro or from micro to macro and we noted a dose-related reduction in the incidence of those progressions.

Now I'd like to turn briefly to talking about

safety in subjects with Stage 3 CKD; individuals with eGFRs between 30 and 60. This dataset comes from four trials that included subjects with eGFRs less than 60, the dedicated study, the DIA3004 Study trial, our CANVAS trial, and two additional trials.

As you can see, there was a modest male predominance. These are older subjects with a mean age, as you can see, of 67 years. Of course, a high incidence of baseline microvascular complications, and quite a long duration of diabetes at baseline -- more than 15 years.

The overall safety profile is shown here. The incidence of any adverse events slightly increased in this population. Adverse events leading to discontinuation, a similar pattern as I described in the broad dataset with no increase in serious adverse events; serious adverse events leading to discontinuation or deaths with canagliflozin treatment.

Now turning to the adverse drug reactions in the Stage 3 CKD population shown here, the incidence of osmotic diuresis related AEs such as thirst, polyuria, or pollakiuria - urinary frequency, was only minimally

increased with canagliflozin. On the other hand, the reduced intravascular volume-related adverse events were increased in a more prominent dose-related fashion than the overall broad dataset, and I identified this before as one of the risk factors for these adverse events.

As I previously commented, even with the dose- related increase in these adverse events, the severity did not appear to be greater in this population. There was no excess of adverse events leading to discontinuation or serious adverse events. Urinary tract infections were slightly increased with canagliflozin in this population.

However, there was no increase in the upper urinary tract infections, serious adverse events, or adverse events leading to discontinuation. General mycotic infections in men and women were increased in this population as in the broad dataset.

Now to summarize a larger body of data with regard to changes in renal function, we did see a larger initial percentage decrease in eGFR with a rise towards, but not to baseline as I showed from our

DIA3004 study. We looked in our CANVAS trial where we had follow-up visits to look at reversibility in the subset of patients with eGFRs between 30 and 60 and saw a similar pattern as I showed in the overall CANVAS trial data.

Outlier analysis showed a similar pattern, which is that when you look at the any time value, you see a higher incidence with canagliflozin reflecting the initial reductions in eGFR. On the other hand, if you look at the last value on study drug treatment, the differences across the treatment groups are quite small.

We did not see an increase in renal-related serious adverse events or adverse events leading to discontinuation, and the decrease in the urinary albumin to creatinine ratio that I showed from the CANVAS trial, the data was similar for DIA3004 dedicated study in patients with CKD.

We saw modest mean increases in serum phosphate and magnesium in this population; modestly higher than seen in the overall population, but with a very low incidence of values meeting outlier criteria

and none reported as adverse events of either hyperphosphatemia or a blood phosphate increase or hypermagnesemia or blood magnesium increased.

We saw only small changes in serum potassium. Hyperkaliemia was infrequent. It was more common on the background of ACE inhibitors, ARBs, or particularly when we saw more severe hyperkaliemia in patients who had multiple risk factors; were on potassium-sparing diuretics, aliskiren, or ACE inhibitors.

Now turning to bone safety, I'll talk a little bit about changes in the calcium access (ph) or results of our bone density assessment and the incidence of fractures. We saw minimal changes in serum calcium and in urine calcium excretion. I mentioned the small increases we saw in serum phosphate and magnesium; these were generally stable over time.

There were transient increases in parathyroid hormone that we saw at week three in our Phase II study, which by week 12 had essentially resolved. We also looked at PTH in our DIA3010 study in older subjects with type 2 diabetes and we noted minimal changes in either of these time points. We also had

PTH values in our study in patients with chronic kidney disease, again the DIA3004 study.

And here we saw small changes relative to placebo over 26 weeks with significant baseline differences in PTH levels. We've seen variable, but overall not meaningful changes in 1,25 and in 25-dihydroxy vitamin D levels as well.

Now I'd like to turn to talking about the changes in bone mineral density that we've seen. Here are the week 52 data done by DEXA and this in the dedicated study in older subjects with type 2 diabetes. As you can see, at the lumbar spine and at the total hip, we saw dose-related decreases in bone mineral density.

These were relatively small and in the femoral neck we saw the opposite trend with a trend toward an increase in bone mineral density. The distal forearm showed no meaningful changes from baseline. Now there's a large body of literature that demonstrates that reductions in body weight are associated with reductions in bone mineral density; so weight loss associated with bone mineral density.

We've done additional analysis to look at this association in our dataset and we find supportive data to demonstrate that the small reductions in bone density at these sites likely reflect the effect of weight loss seen with canagliflozin.

Now I'd like to turn to talking about adjudicated fracture incidents. On the top panel are all adjudicated fractures. As you can see, there was a numerical imbalance, 2.1 compared to 1.6 percent, 2.1 in the all canagliflozin group and 1.6 percent in the non- canagliflozin group.

The 95 percent confidence interval around this difference included zero, indicating that the difference was not statistically significant. We also saw an increase similar in balance in adjudicated low trauma fractures. These are fractures from a standing height or less. Again, 1.6 percent in the combined canagliflozin group and 1.2 percent in the non-canagliflozin control group.

The 95 percent confidence intervals around the difference, again, included zero indicating that this difference would not be statistically significant.

Now looking at the time to event Kaplan-Meier for low trauma fractures, we note that there was an early separation between these treatment groups. As you can see, this occurred within weeks at a time frame when it would be very unlikely reflects differences in bone susceptibility to fracture.

We examined whether this might reflect the effect of the reduced intravascular volume-related adverse events. As you note, there was no evident dose relationship here, although we did see a prominent dose relationship for the reduced intravascular volume-related adverse events.

We had collected narratives in support of the fracture adjudication to review these narratives, and we did not note reports suggesting dizziness or light-headedness. Most of the narratives generally reflected the typical occurrences of falls: trips over objects, curbs, and the like.

We also looked to see whether there was changes in the incidence of falls in the overall program, and the incidence of falls was quite low within both treatment groups. So to summarize, we've

conducted a large Phase III program with more than 10,000 subjects randomized. There was a substantial proportion, about half of our subjects in the broad dataset, from more vulnerable populations.

We found that both doses of canagliflozin were overall well-tolerated with a low rate of discontinuations related to adverse events. The incidence of serious adverse events and deaths was comparable to control. And the safety and tolerability profile was generally similar across the eGFR range above 30.

The specific adverse drug reactions were characterized, which I've discussed in some detail. Specific safety assessments were performed, including the assessment of CV safety and I commented on the hazard ratio of 0.91.

We see small transient and reversible decreases in eGFR consistent with the hemodynamic effect of canagliflozin due to its diuretic action. And I've discussed the small decreases in bone mineral density, which our assessment is that they're related

to weight loss, and the small numerical imbalance in fractures.

I'd like to comment on efficacy before I turn to talking about our dosing recommendations. As we heard earlier, we've seen consistent and sustained dose-related improvements in glucose control with a low incidence of hypoglycemia. We've seen reductions in HbA1c. These have been demonstrated to be non-inferior to glimepiride and to sitagliptin, and superior at 300 milligrams to both agents.

We had a greater proportion of patients achieving the important HbA1c goal of less than seven percent, and we've seen important reductions in fasting and post-meal glucose. We see improvements in beta-cell function, assessed both fasting and post-meal. In addition, we see reductions in systolic blood pressure and in body weight.

With regard to dosing recommendations in patients with type 2 diabetes with an eGFR above 30 who need improved glycemic control, we are proposing 100 milligrams or 300 milligrams of canagliflozin. In those individuals with one of the risk factors that I

identified for the reduced intravascular related adverse events, we would propose a starting dose of 100 milligrams.

If there's an inadequate response in patients started on 100 milligrams, then to increase to 300 milligram dose. I'd like to now ask Dr. John Gerich, Professor Emeritus from the University of Rochester to discuss the canagliflozin benefit risk assessment. Dr. Gerich? Benefit-Risk Review

JOHN GERICH: Thank you, Dr. Stein. Good morning, everybody. As way of background, I've been involved in the treatment of diabetes for over 40 years and have conducted clinical research in the area, and most recently clinical research in the area of the role of the kidney in glucose metabolism.

Now as pointed out by Dr. Horton, over the last 40 or 50 years we've had a large increase in the incidence of type 2 diabetes, so that now it's the leading cause of blindness and kidney failure. On the other hand, we've also had recently the results of several controlled clinical trials that have demonstrated that good glycemic control can markedly

reduce the risk of these macrovascular complications.

For example, this slide illustrates the results from the United Kingdom Prospective Diabetes Study, and it shows that for every one percent reduction in hemoglobin A1c we can reduce the risk of microvascular disease by about 37 percent. Now on the basis of this and other studies, most organizations recommend a treatment goal of a hemoglobin A1c of seven percent or less.

Now I show again a slide that Dr. Horton showed, that illustrates that from the NHANES data that we've improved in achieving this goal recently. However, we still have in general less than 50 percent of patients at goal. So that translates into about 50 percent of patients that are still at increased risk for these macrovascular events.

Now a major factor in our inability to get more patients to goal, are the shortcomings and limitations of presently available drugs. These limitations often relate to two aspects. One is the durability of effect. Over the course of time the efficacy of most of these agents decreases. This is

because of the progressive decrease in pancreatic beta-cell function, insulin secretion.

The other aspect is the side effects of these agents that often limit use of maximally effective doses in patients. The sulfonylureas, DPP4 inhibitors, which depend on functioning beta-cells, lose their efficacy over time. Hypoglycemia is a major rate limiting factor. We see this with sulfonylurea agents and insulin. Many patients reduce the doses of these agents after having an episode of hypoglycemia.

I can speak to this from personal experience, because I did the same thing. We also see weight gain with various agents and most of our patients with type 2 diabetes are obese and we wish they would lose weight, rather than gain weight. Often gastrointestinal side effects limit use of drugs at their maximally effective doses.

And then some agents cause fluid retention and limit their use in people with renal insufficiency and cardiac failure. So we do have a need for additional options to treat our patients. So let's take a look now and see where a drug like canagliflozin

could fit in. It has risks and benefits like other agents. I've listed here the benefits.

As you have seen from the clinical trials that were presented, it has a robust effect on hemoglobin A1c; as good as or better that was seen with sulfonylureas and the DPP4 inhibitors, because it does not depend on beta- cell function. One would anticipate that its effects would be durable. We see this good decrease in hemoglobin A1c with a low incidence of hypoglycemia.

We see that it has a unique mechanism of action that permits it to be used with virtually all other agents in a complementary manner. It improves beta-cell function as you've seen. It causes weight loss rather than weight gain. And additional benefit with it is a reduction in blood pressure which is a known cardiovascular risk factor.

Finally, it is simple to administer a once-a-day dose given orally without any necessary titration or limitations based on liver or renal disease. And the flexible dosing of two doses being available allows individualization, as Dr. Stein mentioned, in certain

populations starting with a low dose and working up. Or if a high-dose, if the 300 is used, it permits reduction in that dose.

Now, one must balance these benefits against risks that have been identified. You've seen that there's an increase in genital mycotic infections. A small increase in urinary tract infections, but I point out these are lower urinary tract infections and they were not associated with severe adverse events.

There was a dose-related higher incidence of reduced plasma volume-related events, a dose-related increase in LDL cholesterol, and a small reduction in bone mineral density. However, I'd like to point out that all of these risks are manageable quite readily in clinical practice.

So let me summarize. With the proposal of canagliflozin we would have flexible dosing with 300 and 100 milligrams to meet individual needs of patients. I think the data has clearly demonstrated a favorable benefit risk profile, and an agent such as canagliflozin should provide a valuable addition to help meet needs of our patients. Thank you. Clarifying

Questions from the Committee

DR. THOMAS: Thank you the presentations. We'll now take clarifying questions from the committee. Just remind the panel members that -- just raise your hand and then we'll keep a list and recognize in the order that you raise your hands. Dr. Hiatt?

DR. HIATT: I have a question for the sponsor on the mechanism of the hypotension, the reduction in blood pressure. So presumably this is primarily mediated by volume depletion, although there is a component of weight loss, reduction in fat mass. So one might assume part of the blood pressure reduction is perhaps related to weight loss.

But in terms of that mechanism and the putative benefits of lowered blood pressure through this mechanism, my question would be how much reflex sympathetic activation is occurring with the hypotension? Through the sponsor briefing document I can't find any specific quantitative definitions of changes in heart rate.

You state they're non-clinically significant. But I guess I'd like to know if you have any data on

changes in resting heart rate. If you have that, it's probably supine or casual heart rate measurements. Do you have any orthostatic measurements of changes in heart rate? And I think maybe stop with that and then follow- up with some of the adverse events related to this.

DR. STEIN: Slide up, so in our Phase III programs, we measured heart rate supine and we didn't see meaningful changes. Generally there was a small trend for a reduction in heart rate in the Phase III trials, but on average, it was really one beat per minute type of range.

This is data from a dedicated study in which patients with type 2 diabetes and all of these subjects were on ACE or ARB therapy as background therapy, and they were randomized to either canagliflozin 300 milligrams or to placebo. And we had them come back to a clinical research center at baseline at week one and then at week 12, and here's results from the orthostatics in that trial.

On the bottom two panels, I'm looking at the difference between standing and supine blood pressure.

This is the orthostatic change and you can see that there were relatively modest differences in orthostatics with systolic and diastolic at either week one or week 12.

In terms of the change from baseline and standing pulse, we saw a small increase at week one and week 12, no notable differences. So that's the information we have with regard to the standing pulse differences.

DR. HIATT: Okay. That's actually very helpful. So you would speculate that at week one the rise in heart rate with standing was related to volume depletion. You think that attenuates by week 12.

DR. STEIN: Yes, and one quick comment. You mentioned earlier the mechanism of the reduction in blood pressure and if I may, perhaps if I could just briefly comment on that, because we have done some initial analysis, if that would be all right.

In the analysis we've done, and we can show some more data if you'd be interested, we estimate that about half of the effect of the blood pressure reduction comes, in fact, from the weight loss, and

about half presumably from the diuretic effect, and I think that might be anticipated. But that, we believe, is the mechanism of the reduction in blood pressure.

DR. HIATT: Okay. And this is an osmotic diuretic effect, whereas a thiazide would be sodium depletion, diuretic effect; so a different mechanism. And the question really I think is, is this mechanism for lowering blood pressure actually clinically beneficial or harmful?

And there's a clustering of these hypotensive intravascular volume events, is your slide 75, which is in the briefing document, figure 26 I think, which is concerning. I mean there's clearly an imbalance at the 300 milligram -- it's a fairly rapid onset event.

And if this is perhaps a biomarker of how the patients are actually doing, then that would suggest that that mechanism of hypotension may be more adverse than say a standard blood pressure regimen to lower blood pressure.

DR. STEIN: I haven't seen similar curves with other diuretic agents, but again, this has a diuretic action, a natural uretic action due to its

osmotic diuresis effect. I think it's important to note that most of these events were mild to moderate intensity as assessed by the investigator and they were generally short-lived. The median duration was between two and six days.

What happened was that many of these patients had adjustments done by their physicians in the concomitant blood pressure lowering medications, reductions or discontinuation of the diuretic dose, other adjustments that were made with resolution of these.

So these tended to be transient events assessed more as mild to moderate, and I think important to note, the occurrence of discontinuations due to these adverse events was quite infrequent and was actually not different than seen in the comparator group.

So our assessment of this is that these events, as you know, occur more frequently, although it's clearly still in a minority of patients, but can be managed. They are transient, manageable, and tend to be more mild to moderate and not more severe events

leading to other complications or problems.

We looked at the crossover of these adverse events, for example, with MACE-plus events and we see a minimal overlap. So these aren't harbingers of the MACE- plus more concerning type of events that we carefully tracked in our program.

DR. THOMAS: Dr. Lewis?

DR. LEWIS: I wonder if you could clarify for me. The mean changes in GFR were expressed plus or minus standard error, which I found hard to -- I don't think it was as informative as perhaps it could have been. Do you have information on, for example, what percent of the patients had a five mL change in GFR? What percent had a 10 mL? What percent had a 30 mL change in GFR?

Similarly, a concern I have is that one of the most common causes of acute renal failure in the hospital is decreased intravascular volume. And I couldn't tell from the briefing document if -- so for example, if a patient who had decreased intravascular volume went into the hospital with pneumonia, which would be the big SAE, they could develop acute renal

failure more likely if they were relatively dry when they went in.

Did you systematically look at ICD 9 codes for acute renal failure as complications of hospitalizations? Now many of these patients could be discharged and have relatively close to what they had in renal function back, but we know that even small decrements in renal functions that are sustained after episodes of acute renal failure would have bad mortality effects later.

So I have two pieces of clarifying information I'd like. Thank you.

DR. STEIN: Certainly. So let me go through a few pieces of data, if I might. Slide up. We started with an outlier analysis and you were asking for more refined cuts which I can also provide. So we'll at the histogram of the changes, which I think gives you the more precise data, but this was the prespecified assessment.

So let me just briefly touch on this, and then I'll show the histograms of changes and then I want to come back to the question about more severe

renal events, did they occur, and how did we assess those.

So the top panel actually looks at the any time post-baseline value and I should say that this is from our broad dataset. So this actually reflects about 16 months of mean duration of exposure. And you can see that there is clearly an increased incidence in the occurrence of patients meeting this criteria, particularly at the 300 relative to the 100, minimally different in the 100 versus the non-CANA group.

We took this criteria based off of the NKF criteria for kidney injury. You can see that the incidence also of the any time values for the greater than 50 percent was also slightly increased with canagliflozin. But then what we did is looked at a last value analysis. So this is actually last on study drug value.

So this is values within two days of the last dose of the study drug. So this is not allowing patients to wash off the effect. This is on the study drug. And as you can see, the incidence of these events is much less frequent; the same in the 100 and

the non-CANA group and only minimally different in the 300 milligram group.

Now with regard to the greater than 50 percent reduction, and I think this feeds into the next question that you were asking about more severe events, we adjudicated all events meeting criteria for greater than 50 percent reductions, doubling of creatinine, last value or sustained, and what I'll show you is the adjudication results that we had.

I should comment that any time a patient was hospitalized, we reviewed the serious adverse event report. So the data that we had for adjudicating events included not just from our central laboratory database, but from serious adverse event reports. So if a patient was hospitalized, we looked to see whether there was a diagnosis of acute renal failure, and then that would have been adjudicated.

Slide up please. So this looks at the numbers of subjects that were submitted for adjudication. You can see it was actually relatively balanced across the treatment groups. Again, I should say this is data from the broad dataset, but we

actually here included all studies to make sure we weren't missing any subjects.

This was adjudicated by an independent, blinded panel, and you can see that the occurrence of events that were considered to be associated with canagliflozin was infrequent and generally similar, probable generally similar to one and one in the non-canagliflozin group and possible again, generally similar.

So this gave us some competence (ph) in the assessment that we weren't seeing events of this greater susceptibility due to the background reduction in plasma volume. Now, I also have the histograms if you'd like to see the more -- oh, okay.

If we can bring up the any time histogram, and then we'll look at the last value, and why don't we pull that up from the broad dataset. So actually let's look at the any time. I think that might be the place to start and then I'll show you when you follow-up, what happens to this.

Great, slide up please. Thank you. So what this is looking at is the change from baseline

distribution and you can see that there is a relatively smooth change in the eGFR, a left shift. And I should set this up by saying that the overlap is the green group, the placebo here is reflecting the placebo group in grey, and then the doses of canagliflozin either the light blue or the darker blue left and right.

And I think what our interpretation of this was, was that there is a clear shift with canagliflozin more prominently with the 100 and 300 milligrams. This is the week six analysis that we did, and I should say that this analysis was from the CV safety study. This is a pretty vulnerable population and certainly a large population as well.

But the numbers of more severe outliers was not notably different, even at this time point across groups. Now if you look at the last eGFR value, slide up please, I think our conclusions were pretty much the same, which is that there is an overlap. You see placebo patients far to the left and canagliflozin patients far to the left, but very infrequently. Most of the changes being in the 10 to 20 percent or zero -- I should say zero to 20 percent range.

So our conclusion from this was that we weren't really seeing a notable, consistent or sustained shift, but we certainly do see a transient shift, which I think reflects the early greater reduction eGFR that I think also, as we've shown, over time tends to either plateau or somewhat attenuate. Does that address your question?

DR. BRITTAIN: The histograms are extremely helpful and I appreciate seeing that. So it better informs me what that mean means. Let me just clarify. The only way you would know someone got acute renal failure from which they might have largely or partially recovered in the hospital, is if the coordinator at the site picked it up and wrote it in on the SAE form.

DR. STEIN: That's correct, but if --

DR. BRITTAIN: Okay.

DR. STEIN: -- of course, we certainly monitored the sites to assure that there was reporting of serious adverse events. It's always possible that something didn't get reported, but we're aggressive in assuring that there is a complete reporting of adverse events.

DR. BRITTAIN: Thank you.

DR. THOMAS: Dr. Knowler?

DR. KNOWLER: Yes, I'd like the sponsor to clarify the situations in which they're proposing this drug be used. A lot of the studies were adding on canagliflozin to other therapy and I think I understand the rationale for that. But if you're also proposing it as initial monotherapy, then really you have to compare that with metformin, which is the standard monotherapy, and I don't remember seeing any studies where you've directly compared those two drugs as monotherapy. Did I miss that or have you done that?

DR. STEIN: No, you're quite correct. We have not done a comparison directly to metformin. Our studies were largely, in fact, on the background of metformin. I would just comment that we want to provide the option to physicians, a fairly broad option of how canagliflozin might be used.

Our expectation though is that it would be used generally consistent with the recent ADA/EASD guideline, which would suggest metformin as initial therapy and then add-on a number of different classes

based upon individualization.

So while we would provide the option, because there are some patients who the physician may feel is appropriate for initial therapy, we think the profile is favorable as initial therapy. But again, I think we would expect that most physicians will follow the ADA/EASD guidance in this regard.

DR. KNOWLER: Could you clarify then, exactly what is it that you're asking for approval for? Is it as monotherapy only, or as add-on, or either?

DR. STEIN: So the specific indication is a more general indication. The standard current indication which is, at use in diabetic patients as an adjunct to diet and exercise. So that's a fairly broad indication which would allow use in monotherapy, add-on to single or dual oral agents, or add-on to insulin. And so we are seeking that broad use, which would cover initial monotherapy as well.

DR. THOMAS: Dr. Brittain?

DR. BRITTAIN: Yeah, I have a couple of questions about the cardiovascular risk data. The first question is, I wasn't quite clear when you -- I

think it's slide CC82, when you talk about the 200 events and then the 500 events and that you were at 200 events in February.

Does that mean you're committed to continuing these trials for -- until you have 500 events? I wasn't quite sure what the future plans were even if there's a potential approval, et cetera. But I also have a second question after that.

DR. STEIN: Sure. So the program that we've put in place is intended to be consistent with FDA diabetes guidelines. So for submission, the demonstration that the upper bound is less than 1.8, and for that analysis we prespecified that it would be conducted when we had 200 events. And as you can see, that's what we did. We had 201 events.

The next part of the guidance indicates that one needs to establish -- this is a post approval part of the guidance -- that we have to demonstrate that the upper bound of the 95 percent confidence interval is less than 1.3. And so we prespecified that that is to be conducted when we get 500 events in the composite. This will be coming from the CANVAS trial, our CV

safety trial, which is an ongoing trial.

We continue to have about 3,300 subjects that are continuing to participate in that trial, but it would include the entire CV meta-analyses population. All other trials would also contribute and it will be conducted when we have 500 events. We estimate that to be in 2015.

DR. BRITTAIN: Okay. My second question is it sounds like you think the hazard ratio is a reasonable index in the CANVAS trial. That you kind of feel that the initial excess risk is, in that first month, was due to just natural variation from month-to-month. But again, I wanted to know, if you do think the hazard ratio is a reasonable index for the treatment difference for the CANVAS study, and I mean it seems like a nice sensitivity analysis would be to compare Kaplan-Meier estimates of survival at some key time points, since that doesn't depend on any (indiscernible) proportionality of hazards. So I was just wondering if you've done anything like that.

DR. STEIN: Yes, we've done some analysis to look at proportionate hazards assumptions and I could

speak about that if that -- is that specifically a question about the proportion hazard assumptions testing?

DR. BRITTAIN: Well, it's related to that, but I guess I'm wondering -- it seems like one way to get around the issue of whether there's proportional hazards is just to look at the Kaplan-Meier curves at key time points and do confidence intervals at six months, one year and either the ratio of survival or proportions, and I wondered if you'd done anything like that.

DR. STEIN: So maybe I could as ask Dr. George Capuano from our biostatistics group to comments specifically. I know he's conducted some sensitivity analysis around this. George?

GEORGE CAPUANO: Dr. George Capuano, Statistics, Janssen R&D. To address your question, I think it's important to step back and just talk briefly about what do we mean by proportional hazards? And it's essentially the constancy of the relative risk over time with respect to treatment. We have done some diagnostics to ensure that this approach is

appropriate. The results suggest that there's no violation of the proportional hazards assumptions.

One of the key ways that we can assess the proportional hazard assumptions is through the use of a test of the interaction with -- of treatment with time in the COX regression model. And slide up -- the P-value for that test is 0.15, not suggesting that there's any issue with the assumptions of proportional hazards.

We also evaluated some of the residual diagnostics; in particular, the smooth Schoenfeld residuals and I can show you those. Other tests that we've conducted, I've mentioned here, are also consistent with the test of the interactions suggesting that the assumptions of proportional hazards has been met.

To your other question, the prespecified analysis was over the entire duration of the trial. So we weren't looking at any individual time point. It's, the proportional hazard assumptions across the entire period. And so we feel that across the entire treatment duration, the assumption has been met.

We have looked at other metrics for relative risk. In particular, a Mantel Haenszel estimate of the relative risk, looking at -- slide up. So we have looked at a stratified Mantel Haenszel relative risk and as well as just the simple odds ratio, and the results are consistent. I would note that the Mantel Haenszel does incorporate the survival time, whereas the odds ratio does not and Mantel Haenszel is non-perimetric.

So given that the point estimates are highly similar to the hazard ratio that we presented, as well as the upper bounds, the 95 percent confidence limit, we're comfortable with these as alternative metrics as well.

DR. BRITTAIN: Just a really quick question. When you presented the results for the proportional hazards, does that refer all the data, not just the CANVAS? Is that --

GEORGE CAPUANO: That's correct. That is the entire dataset, and I'm also happy to walk through the plot of the Schoenfeld residuals -- no.

DR. THOMAS: I think we're okay with that.

Thank you. Dr. Guettier? You had a comment?

DR. GUETTIER: Yeah, for the purpose of full disclosure, the sponsor has partially unblinded the CANVAS trial and you -- I mean I don't know if this is going to be an important consideration.

DR. THOMAS: Thank you. You have a quick question? Dr. Proschan, did you have a comment on the previous questions, or do you have a separate question?

DR. PROSCHAN: It's not a separate question. It's closely related.

DR. THOMAS: So why don't we have you comment?

DR. PROSCHAN: So if you assume that that early, you know that there is an early harm, I'm just wondering what would cause such an early increase in cardiovascular events, what would be the possible mechanisms? I know that you said that there's a lack of association with volume depletion related adverse events. I mean is there anything else that you can think of that could cause that?

DR. STEIN: So as I indicated, our assessment focused on, I think first, just the simple variability

that we observed. Slide up. I think what I would note is that the Kaplan-Meier for the canagliflozin group, as you can see there was perhaps a slightly greater rate in the first 30 days. But I think what is perhaps even more notable is the almost complete absence of events in the placebo group.

If you look at other type 2 diabetes CV outcome studies and we work with colleagues at the George Institute who were kind enough to do this analysis from the ADVANCE trial, what you see is that the rate of adverse events is pretty much a constant over time, and I think that's reflected in most of the Kaplan-Meiers from other CV outcome trials.

And so our assessment of this is that the largest difference here really reflects a very low rate in the placebo group. Which again, I think if you look at any 30-day period, you will see substantial variability. As I showed in this slide when we looked at the month-to-month variability, we noted that in fact the rate in the placebo group, and I think you can see this on the Kaplan-Meier, is dramatically increased from day 30 to day 90.

Slide up. So when you look at the rate in the second and third month, it's actually higher than the rate in the first month in the CANA group. So I think if you are looking for an explanation, I think the higher rate in the placebo group in month two and three would suggest variability is more likely. In terms of associations, the one concern that I think was flagged, which I think is a legitimate concern to raise, is does the diuretic effect of the drug leading to dehydration increase the occurrence of events?

But I would comment that when we'll accept other diuretic outcome trials, one doesn't see, at least as best we can see from the literature, because not much early 30-day data is published, but there's no suggestion of an early delay in the placebo group or an early increase, I should say, with diuretic treatment.

So our assessment of this is that this likely just reflects month-to-month variability.

DR. PROSCHAN: Quick statement. I, you know, I understand everything you said, but I have yet to be involved in a trial that didn't have a placebo rate that was much smaller than what was originally

expected. I mean the same thing happened in the cardiac arrhythmia suppression trial. People said the problem is not that these drugs are killing people; not enough people in placebo group are dying.

DR. STEIN: So if I could clarify that point, because I don't think what we're saying is that the placebo group had unexpected incidents. In fact, the placebo group rate was exactly as we expected. I think what we're saying is that if you look at any 30-day interval in a trial, you will find imbalances.

And so, to look at a trial, the best time point would seem to me to be the prespecified time point, which is what we conducted. And when you look at the prespecified time point when we achieved 200 events, there was no imbalance. In fact, the hazard ratio was below one.

So I don't want to be mistaken to suggest that we're saying that the placebo rate was low across the trial. In fact, it was exactly as anticipated.

DR. THOMAS: Dr. Kaul?

DR. KAUL: Thank you. You said that the cardiovascular program was designed to be consistent

with the FDA diabetes guidance and I'm reading the guidance here. "Meta-analyses should be performed at the completion of Phase II and Phase III trials." And yet, 80 percent of the data is coming from an interim analysis of an ongoing Phase III trial. The guidance also says that "Longer term cardiovascular risk should be assessed, for example, a minimum of two years."

And by my reading of the exposure, it's somewhere between 52 and 65 weeks. So the question, for my own clarification is, is your cardiovascular program faithful to the spirit of the guidance? And then I have follow-up questions.

DR. STEIN: I think that the program is indeed faithful to the guidance. The guidance obviously can be addressed in a number of different ways. The way we had proposed to conduct this was it was from the start to include results from the CANVAS trial. So the CV meta- analysis that was conducted, and that was submitted, was exactly as had been planned which was to have a CV meta- analysis at that time point.

However, I will comment that in the original

design of the CANVAS trial, the intent was to try to keep the CANVAS data blinded and submitted in a blinded fashion. However, when we saw the results from the LDL cholesterol, we felt that it was, as I commented during my presentation, essential to fully understand the CV safety of the drug by looking at and reviewing the results of the CV meta-analysis and so that results were unblinded.

We felt that it would be important for us as well as for the advisory committee to be able to review the results of the CV meta-analysis. Now CANVAS is continuing as a CV safety study to collect very important safety and cardiovascular in general safety information. We believe we have a number of protections in place in the ongoing CANVAS trial.

It's been ongoing, but they're not to subject or to investigator, so it remains double-blinded. We have a blinded adjudication panel, and an independent steering committee, as well as an independent IDMC. So we believe that it was the appropriate step to take and that the CANVAS trial continues and will continue to provide really essential information with regard to

ongoing cardiovascular assessment.

And as I said, this was the way that we had originally planned to do it was, as I indicated, to have data both across our Phase III studies, completed studies, ongoing studies, and including the CANVAS trial.

DR. KAUL: Thank you. I have a follow-up question. Slide 84. And I'm trying to understand how the endpoints were defined and what the clinical relevance is. Now, for example, for fatal and non-fatal MI, there were only two and four fatal MIs. The majority of the MIs were non-fatal. How were they defined? Under what scenarios did these MIs occur? Were they periprocedural? Were they spontaneous MIs? Same thing for stroke. Majority of the strokes were non- fatal. Was there any attempt made to quantify the clinical importance of these strokes? Were they disabling? Were they non-disabling? And then also the unstable angina -- the unstable angina requiring hospitalization data favors the canagliflozin.

And what led to these hospitalizations? How many of them were associated with EKG changes, wall

motion abnormalities on an echo, or evidence of ischemia, or coronary disease on angiography? How many of them ended up getting revascularized? I'm trying to understand the clinical importance of these events. Thirty-seven out of the 44 unstable angina events were reported from CANVAS.

Was this a prespecified outcome of interest in CANVAS? Were investigators asked to report unstable angina leading to hospitalization?

DR. STEIN: So with regard to -- let me make a few comments with regard to the questions you're asking. The criteria that we applied were standard criteria that the adjudication committee applied to the assessment of these events, and we can review the specific adjudication criteria with you, to see how each of these events was defined.

It was defined, pre-specified definitions that were then applied by this blinded adjudication panel. You asked about the outcomes. We did not look at an analysis of the outcomes of stroke or the outcomes of unstable angina, so I'm not sure I can provide you currently with analysis of the downstream

outcomes of unstable angina or stroke.

I can comment that the inclusion of the unstable angina was because it's in the spectrum of myocardial infarction and hence, we felt it was a useful risk indicator. But I would also comment that the results from our analysis of MACE and MACE-plus were quite similar, in any case.

DR. KAUL: Was it a prespecified outcome in the CANVAS trial?

DR. STEIN: Yes, it was a prespecified endpoint for the safety assessment for this composite endpoint. All four of these endpoints were prespecified and the investigators were to flag any of these events that they identified. There was a case report form that they would check if a subject had such an event.

In addition, we reviewed all adverse events reported to determine whether any other terms were suggestive of any of these types of events, and if they were those were also submitted for adjudication to the blinded, independent adjudication committee.

DR. THOMAS: Dr. Cooke?

DR. COOKE: Just a simple question. In the

safety studies in the broad dataset, the DS3, why was the sitagliptin study not included in that data? I think it was the 3015?

DR. STEIN: The broad dataset included all studies that had both doses of canagliflozin, to try to keep the exposures across these groups comparable. So in our materials for filing, we provided detailed information separately about the DIA3015 trial, and we'd be happy to provide separate safety assessment results, if you'd like to see specific information.

The results were generally similar to the overall program, for the specific reason was that we prespecified inclusion of all studies that included both doses and their control group.

DR. THOMAS: Dr. Capuzzi?

DR. CAPUZZI: Yes. I, after all the discussion, I don't want to prolong this with anything esoteric. But even after the reading of the protocol there was -- I liked a lot of what I saw, but one thing I had some questions about. And this is -- in diabetes itself, you have a tendency to glycation and oxidation to molecules, and this interferes with receptor uptake

just by obliterating the charge.

So you have a situation here where you have not only slight increases in LDL cholesterol, which could be meaningful, but even the particle number, it was checked by NNMR. That's a much more sensitive test and the particle number was increased. That's a problem.

So all I'm saying is that diabetes itself, even without this drug, tends to produce oxidation and glycation. And the higher the triglycerides are, the more numerous the particles of LDL are, okay? So there has to be some kind of a plan to address this. Otherwise, the issues of macrovascular disease which were brought up, this might be the way to look at them and deal with them, and I'm not going to say anything more than that. But that's a really big issue in my mind.

DR. STEIN: As I, I guess what I might note here is that we've seen effects on a diverse range of cardiovascular risk factors with canagliflozin. As you point out, the increase in LDL, the increase in particle number was relatively smaller than the

increase in LDL. But I'd also point out that we saw improvements in another validated cardiovascular risk predictor, which is improvements in blood pressure, and effects on a range of other cardiovascular risk factors.

So our assessment of that was that the best way of understanding sort of the integrated effect of these diverse effects on the cardiovascular risk factors, was to look at the results of the cardiovascular meta- analysis, which I've shared with you, where we see a hazard rate that is below one with a confidence interval upper bound 1.22.

Clearly, we continue to need to look at longer time points for those analysis which are, as I indicated, will be conducted.

DR. CAPUZZI: Well, thanks for what you said, but what we're talking about is something very basic to the regulation of blood sugar. The blood pressure is way up here in the macro area. And this is something that, nothing that you've said, I don't want to say this, but nothing that you've said that really gets to this point, which is really important. It's that

glycation and oxidation -- and this isn't esoteric, it's known for years and it's shown here.

DR. THOMAS: We'll now take a 15-minute break. Panel members please remember that there should be no discussion of the meeting topic during the break amongst yourselves or any member of the audience. We'll resume at 10:30 a.m. And after the FDA presentation, if there is time after questions, the FDA will resume to questions from this morning, or later this afternoon we should have some time as well. Thank you.

(A recess was taken.)

FDA PRESENTATIONS

DR. THOMAS: We will now proceed with our presentation from the FDA. I'd like to remind public observers at this meeting, that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Canagliflozin: Clinical Efficacy and Safety

DR. KWON: Good morning, ladies and gentlemen. My name is KC Kwon and I'm a clinical

reviewer in the Division of Metabolism and Endocrinology Products. I'll be presenting the clinical efficacy and safety issues related to canagliflozin.

This is the outline of my presentation. The sponsor has already discussed the overall efficacy related to canagliflozin and I'd like to focus on the efficacy in the context of renal impairment, since it will be an important consideration as we look at the benefit risk in this specific patient population.

Then I will discuss the following main safety issues related to canagliflozin, which include volume depletion events, renal safety issues, bone safety findings, genital mycotic infections and cardiovascular safety. I will conclude with an overall summary.

As the sponsor has already discussed, canagliflozin is an SGLT2 inhibitor. By inhibiting the sodium glucose co-transporter 2 in proximal tubule, canagliflozin lowers the renal glucose threshold which is the plasma glucose concentration that exceeds the maximum glucose reabsorption capacity of the kidney.

Lowering this threshold leads to increased

urinary glucose excretion. Therefore, the efficacy of canagliflozin is dependent on both the plasma glucose level and renal function. Now I've discussed the efficacy related to renal impairment with canagliflozin.

This figure is taken from trial DIA1003, which was a pharmacokinetic and pharmacodynamic study in patients with various levels of renal function. The figure shows the change in the urinary glucose excretion over 24 hours on the Y-axis, as a function of estimated GFR, after a single 200 milligram dose of canagliflozin.

The green rectangle highlights patients with normal renal function. The blue, red, and orange rectangle highlights patients with mild, moderate, and severe renal impairment. The graph shows that as renal function declines, there is a decrease in the total amount of glucose excreted in urine over a 24-hour period.

In order to assess the impact of renal function on canagliflozin efficacy, patients with moderate renal impairment were pooled from Phase III

trials as shown in the left table. The biggest contributor to this pool came from a subset of the cardiovascular outcome study, DIA3008 or CANVAS.

In this study, the study allowed patients with baseline estimated GFR of 30 mL per minute or greater to enroll. All patients from the dedicated study in patients with moderate renal impairment, DIA3004, were part of this pool.

Only about a thousand out of 10,000 patients in the canagliflozin group had moderate renal impairment. The glycemic efficacy of canagliflozin in this pooled group of moderate renal impairment can be compared to the pooled group of placebo-controlled studies as shown on the right. The patients in this pooled group of placebo- controlled studies had normal to mild renal function.

As you can see from the tables, there is some overlap of patients between these two pooled datasets, but this overlap is small and unlikely to have a significant impact in the overall results. This table summarizes the baseline characteristics of treatment groups for the two pooled efficacy datasets that were

discussed in the previous slide.

Both groups of canagliflozin, 100 milligram and 300 milligram, are combined in this table since there was no significant difference between them. In yellow, the characteristics for the moderate renal impairment datasets are shown. The mean estimated GFR for this population was 48 mL per minute at baseline.

The characteristics for the placebo-controlled studies dataset are shown in white. The mean estimated GFR for this population was 81 mL per minute at baseline. We will refer to the pooled placebo-controlled studies as normal to moderate renal function, since almost 90 percent of this pool had baseline GFR of 60 or greater.

In addition, there are some other notable differences between these two populations. The subjects in the moderate renal impairment dataset were slightly older and had a longer duration of diabetes compared to those with normal to moderate function.

This graph and table show the placebo-adjusted point estimate and 95 percent confidence interval for the least (ph) squares mean change in

hemoglobin A1c from baseline for each dose of canagliflozin for two populations as defined by baseline renal function.

The zero on top of the Y-axis indicates that there is no difference between treatment groups and there is a better efficacy as the point estimate moves further down from zero in this graph, since that would indicate a larger reduction in hemoglobin A1c.

The red color represents the placebo-adjusted hemoglobin A1c change in patients with moderate renal impairment, and blue represents the placebo-adjusted hemoglobin A1c change in patients with mild to normal renal function. The figure shows that canagliflozin offers significantly less glucose lowering benefit in patients with moderate renal function, compared to patients with mild to renal function.

Moderate renally impaired patients had a hemoglobin A1c reduction of 0.4 to 0.5 percent, and mild to normal renal function in patients had a hemoglobin A1c reduction of 0.7 to 0.8 percent.

The graph and table in this slide present data for two subgroups of patients with moderate renal

impairment. Here the red again shows that placebo-adjusted hemoglobin A1c change in the overall pool of moderate renal impairment which was presented in the previous slide.

In order to assess the consistency of glycemic benefit across the range of renal impairment represented in this patient population, we formed two subgroups based on estimated GFR: less than 45 mL per minute, and greater than or equal to 45 mL per minute.

The blue shows the hemoglobin A1c change in those with baseline GFR of less than 45, and black shows the hemoglobin A1c change in those with baseline GFR of 45 and greater. You can note that about a third of the overall moderate renal impairment group had baseline GFR of less than 45, and although it did reach statistical significance, the glycemic response was modest at the lower dose of canagliflozin in this subgroup, compared to the glycemic efficacy that was observed in the overall pool.

Two-thirds of the moderate renal impairment group had baseline GFR of 45 and greater and appeared to be the main contributor to the glycemic efficacy

that was seen in the overall pool of moderate renal impairment.

In summary, these data provide evidence that glycemic efficacy of canagliflozin decreases with declining renal function.

Now I'd like to present safety issues related to canagliflozin. This table again summarizes the pooled datasets that the sponsor presented that were used for safety assessment in the canagliflozin program that will be presented in my presentation.

The first one is the placebo-controlled studies dataset for DS1, which pooled patients from four placebo- controlled studies with a primary assessment time point at 26 weeks. The second one is moderate renal impairment dataset or DS2, which pooled patients with baseline GFR of 30 to 60 mL per minute.

The broad dataset or DS3, included patients from all eight placebo and active-controlled studies, and placebo and active treatment groups were combined into a non-canagliflozin group as a comparator to canagliflozin group.

It should be noted that the DS3 data that I'm

presenting is slightly different from the sponsor's DS3 data, since I used DS3 that was submitted at the time of NDA submission with the cutoff date as shown in this table, whereas the sponsor's DS3 included all data up to July 1st, 2012.

This table summarizes the baseline characteristics across the three pooled datasets. Patients in DS1, the pool of placebo-controlled studies, were younger compared to patients in DS2 and DS3. Recall that DS2 and DS3 included patients from cardiovascular outcome study DIA3008, the renal impairment study DIA3004, and older adult study DIA3010.

Some of the differences are highlighted here in red and the pool of moderate renal impairment or DS2 not only had the worst baseline renal function, but also had the longest duration of diabetes, and more comorbidities at baseline compared to DS1. Similar findings were seen in patients in the broad dataset or DS3.

This table summarizes the overall mean exposure across three pooled datasets. The table shows

that the broad dataset, or DS3, had the largest and longest duration of exposure. As noted, canagliflozin increases urinary glucose excretion and acts as an osmotic diuretic, which could lead to adverse events related to reduced intravascular volume.

In the next several slides, I will discuss volume depletion events. Changes in systolic blood pressure are relevant to volume status, and patients with renal impairment are expected to be more sensitive to changes in volume. The two figures presented here in two different patient populations with different baseline renal function.

The mean systolic blood pressure changes are presented for the placebo-controlled studies dataset, DS1 on the left, and these patients had mild to normal renal function. The changes from the dedicated trial in patients with moderate renal impairment, DIA3004, are presented on the right, and the reduction in systolic blood pressure with canagliflozin was seen at the earliest ascertained time point in both patient populations.

The figures also suggest that patients with

moderate renal impairment are more sensitive to blood pressure reduction with canagliflozin as shown on the right. Similar changes and trends were observed with diastolic blood pressure with smaller magnitude of change compared to systolic blood pressure.

To search for adverse events possibly related to volume depletion, the safety dataset was searched using the preferred terms indicative of volume depletion as shown in this slide.

This graph presents the incidence of volume depletion events by treatment group in DS1, DS2, and DS3. The green bar shows the incidence in placebo; the blue shows canagliflozin 100, and the red shows canagliflozin 300 milligram. The incidence of volume depletion events was not increased with canagliflozin in the pool of placebo-controlled studies or DS1.

In the pool of moderate renal impairment, DS2, and in the broad dataset DS3, the incidence of volume depletion events were dose dependently increased. The increased incidence of volume depletion events with canagliflozin was most notable in the pool of moderate renal impairment or DS2, where the

incidence was two-fold higher with 100 milligram dose and three-fold higher with 300 milligram dose of canagliflozin compared to placebo.

Most of the reported volume depletion events were hypotension and postural dizziness. This figure shows the Kaplan-Meier curve of time to first volume depletion event for treatment groups in the pool of moderate renal impairment. The bottom line shows the curve for placebo, and the line above that is the curve for canagliflozin 100 milligram, and the top line shows the curve for canagliflozin 300 milligram.

The figure shows that the volume depletion events were dose dependent and occurred early on, within six weeks or initiating canagliflozin. In order to assess the risk factors for volume depletion events with canagliflozin, a subgroup analysis based on baseline characteristics were done in DS3.

Part of the results of this univariate analysis are shown here. Based on this subgroup analysis, there was about two to three-fold increase in volume depletion events with canagliflozin 300 milligram, compared to non- canagliflozin in the

subgroups highlighted here in blue in patients with baseline GFR of less than 60 mL per minute, elderly who were 75 years and older, and those who were also on loop diuretics.

Based on this analysis, the sponsor proposed initiating canagliflozin at 100 milligram dose in patients with any of these risk factors, and increasing to 300 milligram if additional glycemic control is needed. However, it should be noted that it was not prospectively evaluated whether this titration approach would minimize the risk of volume depletion events.

In other subgroups shown here in red, such as use of ACE or ARB at baseline, in particular combined with diuretics, lower systolic blood pressure, and longer duration of diabetes, also suggests two to three-fold increase in the incidence of volume depletion events with the higher dose of canagliflozin, 300 milligram, compared to non-canagliflozin.

Since canagliflozin can cause decrease in blood pressure, one would expect compensatory increase in heart rate. These two graphs show the mean change in heart rate over time in DS1, patients with mild to

normal renal function on the left, and for study 3004, in patients with moderate renal impairment on the right.

Again, green represents placebo; blue represents CANA 100; and red presents CANA 300 group. There is an overall trend showing decrease in heart rate with canagliflozin in DS1. There was no clear pattern in heart rate change with canagliflozin in patients with moderate renal impairment.

We also explored whether electrolyte changes and volume changes will lead to increased incidence of rhythm disorder. We conducted a broad search for cardiac arrhythmias using the preferred terms shown in this slide, including the preferred term, palpitations.

One hundred and ninety-seven cases were identified using this search strategy in the largest pool for safety, DS3. Using this strategy, we did not find a large imbalance in these type of events with canagliflozin. Note that in this table the incident did not account for potential differences in patient exposure.

Next we will discuss renal safety. In the

Phase I trials of canagliflozin there was an early increase in urine volume, serum creatinine, albumin levels, along with decrease in blood pressure. In Phase III trials, as I will show in the next three slides, there was an early and dose-dependent decrease in estimated GFR with canagliflozin, with correlated increase in BUN and serum creatinine.

This figure shows the mean change in estimated GFR over time in the placebo-controlled studies dataset or DS1, who had normal to mild renal function. For the next several slides, again the placebo is shown in green, CANA 100 is shown in blue, and CANA 300 milligram is shown in red. The largest decline in GFR with canagliflozin occurs at the earliest ascertained time point at week six, with gradual return to near baseline over duration of the study.

And you can also see that the decrease in GFR was dose-dependent. This figure shows the mean change in estimated GFR over time in patients with moderate renal impairment from study 3004. Again, you see the largest decline in GFR with canagliflozin at the

earliest ascertained time point, which was week three in this trial.

But unlike those in DS1 who had normal to moderate renal function, the decline in GFR appeared to persist over time. And although there's an initial dose- dependent increase in GFR at week three, by the end of week 26, the overall decline in GFR was similar in magnitude between the two doses of canagliflozin compared to placebo.

This figure shows the mean change in estimated GFR over time in patients at a high cardiovascular risk who are enrolled in the cardiovascular outcome trial, DIA3008. This trial also had the longest duration of follow-up, although the number of subjects drop-off significantly after week 39.

Similar to previous two graphs, the largest decline in GFR occurs early. And similar to figure from study 3004 in patients with moderate renal impairment, this decline was dose-dependent and does not appear to reverse. 3008 study also enrolled patients with baseline GFR as low as 30 mL per minute,

and the mean baseline GFR was 77 mL per minute.

In summary, these three graphs show that the magnitude and pattern of change in GFR is different, in different patient populations studied. This graph and table shows the treatment effects on the incidence of significant renal function changes, defined as GFR more than 30 percent reduction from baseline at any time.

Incidences from three datasets are presented in this slide: DS1, DS2, and DIA3004. Patients in DS1 again had normal to moderate renal impairment. DS2 and 3004 both included patients with baseline renal impairment, but the overall renal function was slightly worse in 3004 compared to DS2. The mean GFR was 40 mL per minute in DS2 and 40 mL per minute in 3004.

As shown in the figure, there was a dose dependent increase in the incidence of significant renal function changes with declining renal function from DS1 to DS2 to DIA3004. This graph shows the incidence of patients with more than 50 percent GFR reduction from baseline at any time and again show that there is an increased incidence of more marked (ph) renal function changes with canagliflozin as reflected

in the higher incidence with canagliflozin in 3004, compared to DS2 or DS1.

These data indicate that compared to patients with relatively well-preserved renal function, patients with moderate renal impairment appear to be at an increased risk for developing more market changes in renal function with canagliflozin. And the long-term renal consequences of these observed changes in renal function with canagliflozin are unknown.

These two figures show the mean change in potassium time over time with mild to normal renal function in DS1 on the left, and patients with moderate renal function from 3004 on the right. Commensurate with changes in GFR, the largest increase in mean serum potassium levels with canagliflozin was seen at the earliest ascertained time point, and this increase was more pronounced in those with renal impairment as shown on the right. The rising potassium returned to near baseline levels over time in both patient populations.

These two figures show the mean change in serum potassium over time in two subgroups of patients

by baseline use of ACE inhibitor or ARB agent in study 3004. Figure on the left show the potassium change in patients who are not on ACE or ARB, and the figure on the right shows the potassium change in patients who are on ACE or ARB agents at baseline.

There was a larger increase in the mean serum potassium levels with canagliflozin in patients who were also on ACE inhibitor or ARB agent. These two figures show the mean change in serum potassium over time in two subgroups of patients by baseline use of potassium- sparing diuretics from study 3004.

The figure on the left shows the potassium change in patients who are not on potassium-sparing diuretics; the figure on the right shows the changes in patients who are on potassium-sparing diuretics. There was a larger increase in the mean serum potassium levels with canagliflozin in patients who were on potassium- sparing diuretics. This graph and table presents the incidence of hyperkaliemia-related adverse events in DS1 and DS2.

There is an increased incidence of hyperkaliemia events with canagliflozin in patients

with moderate renal impairment, DS2, compared to patients with mild to normal function, DS1. And this increased incidence appeared to be dose-related. I will now focus on renal related adverse events.

The sponsor identified renal related adverse events by searching the safety dataset using the standardized MedRA query for acute renal failure, in addition to blood creatinine increase, and GFR decrease, preferred terms. The standardized MedRA query for acute renal failure included the preferred terms listed in this slide.

This graph and table summarizes the incidence of renal related adverse events in DS1 and DS2. Consistent with significant change analysis in GFR shown earlier, the incidence of renal related adverse events was higher in patients with moderate renal impairment, DS2, compared to patients with mild to normal renal function in DS2.

Also, the incidence of renal related adverse events was higher with both doses of canagliflozin compared to placebo in patients with moderate renal impairment. In summary, the available data suggests

that the larger treatment effect in GFR by canagliflozin places patients at an increased risk for clinically significant renal related events.

Next, we'll discuss bone findings related to canagliflozin. This slide summarizes non-clinical bone related findings in rabbits. Dose dependent hyperostoses was seen in rats with canagliflozin. There was an increase in urinary calcium excretion, decrease in serum parathyroid hormone, 1,25 dihydroxy vitamin D, and bone turnover markers.

In DIA2001, a 12-week Phase II dose finding trial, an increase in bone reabsorption marker beta-CTX, was seen with canagliflozin compared to placebo. There was 23 to 30 percent increase with canagliflozin compared to nine percent in the placebo group, which was observed by week three and persisted to the end of the study.

There was no consistent changes in bone formation markers, an increase in parathyroid hormone that was not dose dependent, along with a slight decrease in vitamin D metabolites. An increase in urinary calcium was not observed. In the pooled

dataset of placebo- controlled trials or DS1, there was a slight overall increase in the mean serum calcium levels with canagliflozin compared to placebo and this was dose dependent.

The mean increase in serum phosphate was larger and was also dose dependent with canagliflozin compared to placebo. This table summarizes changes observed in the calcium regulatory access from dedicated moderate renal impairment trial, DIA3004. There was a moderate increase in 25 dihydroxy vitamin D with canagliflozin, compared to placebo.

Paradoxically, there was a slight decrease in 1,25 dihydroxy vitamin D level with canagliflozin. The mean serum parathyroid hormone decreased with canagliflozin compared to placebo. And similar to what to what was observed in DS1, there was a slight increase in serum calcium and phosphate levels with canagliflozin.

These two figures show the mean change in serum calcium over time in DS1 on the left, and 3004 study on the right. Again, the placebo is shown in green, CANA 100 in blue, and CANA 300 in red. In DS1,

there was an early rise in calcium levels which was dose dependent. There was a wide variation in calcium changes from study 3004.

These two figures show the mean change in serum magnesium over time in DS1 on the left, and 3004 study on the right. Again, the rise in serum magnesium was dose dependent and was seen at the earliest ascertained time point with canagliflozin compared to placebo, and this was seen in both patient populations.

A larger increase in magnesium levels with canagliflozin was seen in patients with moderate renal impairment. These two figures show the mean change in serum phosphate over time in DS1 on the left, and 3004 study on the right. Similar to changes in magnesium, there was an early rise in phosphate level with canagliflozin which was dose dependent, and a larger increase in phosphate levels with canagliflozin was observed in patients with moderate renal impairment.

DIA3010 was a dedicated bone safety study in older patients that is still ongoing. The trial evaluates bone turnover markers and bone mineral

density, and included patients aged 55 to 80 years of age with osteopenia. About 700 subjects were randomized to three treatment groups, and the randomization was balanced.

The study included a 26-week core double-blind period, followed by a 78-week double-blind extension period, and at the time of NDA submission, 20-week results were submitted. The applicant submitted 52-week interim data at the end of November. This table summarizes the placebo-adjusted changes in bone turnover markers, as well as change in estradiol and parathyroid hormone levels at 26 and 52 weeks.

Except for serum CTX and serum P1NP at 26 weeks, the other values were assayed from archived serum samples. In DIA3010, consistent with Phase II trials, there was a mean increase in bone reabsorption marker, beta CTX with canagliflozin compared to placebo, which was statistically significant at both doses at 26 and 52 weeks. There was a smaller, non-significant decrease in one of the bone formation marker, P1NP, at 26 weeks.

An increase in another bone formation marker,

osteocalcin, with both doses of canagliflozin, reached statistical significance by 52 weeks. The serum estradiol levels decreased during the study and the serum parathyroid hormone increased during the study. The bone mineral density was measured at four sites in the 3010 study: lumbar spine, distal forearm, femoral neck, and total hip, and this table summarizes the observed changes at 52 weeks.

The bone mineral density measure decreased at lumbar spine and at total hip with both doses of canagliflozin, which achieved statistical significance at the higher dose of canagliflozin. This table summarizes the changes in bone mineral density measured by quantitative CT at 52 weeks.

The observed changes in bone mineral density by quantitative CT was consistent with DEXA results. And the decrease in bone mineral density measured in lumbar spine and total hip reached statistical significance with the higher dose of canagliflozin. The sponsor prospectively adjudicated all fractures reported in the Phase III trials and the fractures were adjudicated and classified by location and by trauma

classification as shown here by high trauma, low trauma, pathological, stress, and other factors.

This table shows the total reported fractures regardless of adjudication as of July 1st, 2012. As there was no indication that the incidence of fractures were dose dependent, events in both doses of canagliflozin were combined into all CANA group and was compared to non-CANA group. The overall incidence of reported fractures was higher in the combined CANA group, compared to non-CANA group, and approached statistical significance.

When this incidence was adjusted by patient exposure, the difference between treatment groups did not reach statistical significance, but the imbalance in fractures not favoring canagliflozin remains. This table shows the adjudicated fractures by skeletal region and trauma classification as of July 1st, 2012.

After adjudication, the imbalance in fractures now favoring canagliflozin is still observed, and this imbalance in fracture was mainly seen in the upper limb in both overall fractures and in low trauma fractures. This is highlighted in red here.

There was also an imbalance in the spine fracture, although the number of reported events was very small. We consulted bone experts within FDA in the Division of Reproductive and Urologic Products, and the clinical reviewer, Dr. Stephen Voss, reviewed fractures in DS4, which is the same dataset as DS3, except with the data cutoff of January 31st, 2012.

Dr. Voss reviewed fractures, excluding non-fragility sites such as hand, fingers, foot, toes, skull, facial bones, scapula and patella. These analyses also show the imbalance in the upper limb fracture not favoring canagliflozin, and he also noted that some of the fractures that appeared to be increased with canagliflozin, such as humerus, wrist, and spine could be indicative of bone fragility.

This graph shows the Kaplan-Meier curve of time to first low trauma fracture event. The curve for CANA 100 and 300 milligram appeared to converge, again demonstrating that there was no dose dependent increase in fractures with the higher dose of canagliflozin. The increased incidence in the lower trauma fractures with canagliflozin compared to non-canagliflozin group,

appear to occur as early as 12 weeks where the separation of blinds occur.

Because the increased incidence of fractures with canagliflozin appears to occur early, it is feasible that these fractures, especially the upper limb fractures, are possibly related to falls due to volume depletion events such as hypotension. In order to assess this, we searched for falls in the large safety database using the specific adverse event term, fall. The result of this search as presented in this slide suggest that falls with canagliflozin was not increased compared to non-canagliflozin.

However, the search strategy using just the preferred term, fall, is limited. The investigator reported terms for adverse events are verbatim terms which are coded to a standardized medical terminology preferred terms for safety assessment. Based on our review of reported terms, some of the verbatim terms that were indicative of falls, were not coded as fall as shown in this table.

So we conducted a broader search to identify all events including dose where the verbatim terms

contained the word, fall, fell, or collapse. Our broader search showed that although the overall incidence was low, there was a slight increase in the incidence of falls with canagliflozin, compared to non-canagliflozin group as shown in the table on this slide.

This curve shows the time to first fall. The increased incidence of canagliflozin compared to non-canagliflozin group occurs early, as shown by separation of curves around 50 days. As increase in urinary glucose excretion caused canagliflozin may potentially increase fungal growth in the perineum, genital mycotic infections were events of special interest.

To search for female genital mycotic infections, the safety dataset was searched using the preferred terms shown in this slide. The incidence of female genital mycotic infections in DS1, DS2, 3010 and 3008 are presented in this table.

Incidences from study 3010 and 3008 are relevant, since 3010 included older subjects, and 3008 included patients with longer duration of diabetes,

more comorbidities, and also had the longest duration of follow-up.

The incidence of female genital mycotic infections was higher with canagliflozin for all datasets and was not dose dependent. There was three-fold higher incidence with canagliflozin compared to placebo in DS1, and five to seven-fold higher incidence with canagliflozin compared to placebo in DS2, study 3010, and 3008.

This slide describes some of the characteristics observed with female genital mycotic infections. The most commonly reported terms were vulvovaginal candidiasis and vulvovaginal mycotic infections. The recurrence was higher for canagliflozin; 22 percent compared to 10 percent in placebo.

The use of antifungal therapy and dual antifungal and antibacterial therapy was higher with the canagliflozin group compared to placebo group. The overall mean duration of vulvovaginal events was longer with canagliflozin; 38 days with canagliflozin,

compared to 16 days with placebo.

To search for male genital mycotic infections, the safety dataset was searched using the preferred terms listed in this slide. The incidence of male genital mycotic infections in DS1, DS2, 3010, and 3008 are presented in this slide. The incidence of male genital myotic infections was higher with canagliflozin compared to placebo.

There was six to seven-fold higher incidents with canagliflozin compared to placebo in DS1, and nine- fold higher incidence when adjusted for subject exposure and this was not dose dependent. The increased incidence of male genital mycotic infections in 3010 and 3008 were dose dependent.

There was six to seven-fold higher incidents with canagliflozin 300 milligram compared to placebo. The relative incidence in patients with moderate renal impairment, DS2, was slightly lower compared to other datasets.

This slide describes some of the characteristics observed with male genital mycotic infections. The genital mycotic infections in men

occurred more in uncircumcised men or men with prior history of genital mycotic infections.

Similar to women, the recurrence rate was higher with canagliflozin; men, 22 percent with canagliflozin compared to none with placebo. The use of antifungal therapy to treat general mycotic infections in men was also higher with canagliflozin, and the overall mean duration of balanitis was longer with canagliflozin; 40 days compared to 16 days in placebo.

There was an imbalance in the number of patients on canagliflozin reporting phimosis from study DIA3008. Phimosis is a condition where in men the foreskin cannot be fully retracted over glans. Four of these nine events were serious, and one required circumcision.

Next, I'll discuss issues related to cardiovascular safety. There was a dose dependent increase in LDL cholesterol level with canagliflozin. Comparator adjusted LS mean percent change in LDL across all Phase III trials ranged from 2.2 percent reduction, to 8.5 increase with 100 milligram dose of

canagliflozin, and 2.8 to 12 percent increase with 300 milligrams of canagliflozin.

This increase in LDL was seen at week 18 and persisted until the end of study. The LDL levels in these studies were calculated using Friedwald equation in these trials, and directly measured LDL in study 3005 and 3006 were consistent with the calculated LDL levels.

The proportion of subjects who initiated statin therapy during the core trial period was small and balanced between two main groups and did not appear to affect the results.

This graph shows the measurement of Apo B by treatment group from two studies; 3005 on the left, 3006 on the right. Again, the green is placebo, the blue is CANA 100, and red is CANA 300. The results show that there was a dose dependent increase in Apo B levels, suggesting that LDL level increase with canagliflozin is due to an increase in particle numbers.

This table shows placebo-adjusted. These squares mean percent change of LDL cholesterol particle

by NMR from study 3006. The results show that the increase in LDL was largely driven by an increase in the amount of large LDL particles.

This figure presents the overall change in lipid parameters in the pooled datasets of placebo-controlled trials. Again, green shows placebo, blue shows CANA 100, and red shows CANA 300. The figure shows that there was a dose dependent increase in LDL, non-HDL, and HDL levels with canagliflozin compared to placebo.

An increase in triglyceride level was seen with placebo, and a slight increase in CANA 100 without any change in CANA 300 milligram. This table presents the results of cardiovascular meta-analysis showing the hazard ratio of the overall MACE-plus events and its individual component.

The results and methodology for this cardiovascular meta-analysis will be presented by Dr. Mat Soukup following my presentation, and I'll just briefly discuss the overall finding. The prespecified MACE-plus did not show an increased incidence of cardiovascular events with canagliflozin as the hazard

ratio was 0.91.

When you look at individual components of MACE- plus, the point estimate for stroke is greater than one and 1.46, although the 95 percent confidence interval is wide and crosses (ph) one. Most of the strokes were ischemic.

In the cardiovascular outcome study, DIA3008 or CANVAS which enrolled patients at a high-risk for cardiovascular events, an imbalance in the MACE-plus events was observed during the first 30 days after randomization.

Thirteen MACE-plus events occurred with canagliflozin, compared to one MACE-plus event with placebo. These 13 MACE-plus events with canagliflozin was evenly distributed between the two doses of canagliflozin; seven with 100, and six with 300 milligram, and this included six strokes, five MIs, and two hospitalization for unstable angina.

Because these cardiovascular events occurred early, we considered whether volume depletion events which occur early with canagliflozin may have led to this observed imbalance. The provider narratives for

these 13 events with canagliflozin did not have sufficient detail to assess the volume status before or at the time of cardiovascular event.

We also assessed whether there are possible risk factors that may have predisposed certain patients to have early cardiovascular events. And so we compared the baseline characteristics for patients who experienced MACE-plus events during the first 30 days with CANA, after 30 days with CANA and those who had CV events with placebo.

There was a slight imbalance in the baseline characteristics among these three groups in the cardiovascular history and risk factor, but the numbers were small and inconclusive.

So in summary, the glucose lowering efficacy of canagliflozin decreases with worsening renal function, and canagliflozin, as we saw, was associated with a decrease in renal function as measured by estimated GFR. In subjects with moderate renal impairment, canagliflozin was associated with an increased risk of significant renal function changes, renal related adverse events, and hyperkalemic events.

And the elevation in the mean potassium levels with canagliflozin was more pronounced at the earliest time point with patients who are concurrently on ACE inhibitor or ARB, or potassium-sparing diuretic, more susceptible to this increase.

Canagliflozin was associated with an increased risk for volume depletion events, most commonly hypotension. In patients with moderate renal impairment, advanced age, advanced disease stage, and on therapies to treat comorbidities, appeared to be particularly susceptible to volume depletion events with canagliflozin.

The timing of these volume depletion events coincided with reductions in systolic and diastolic blood pressure, which was observed at the earliest ascertained time point in Phase III trials. Canagliflozin was associated with a rise in markers of bone turnover.

And it was associated with a consistent dose dependent small increase in mean serum phosphate and magnesium, and a relatively small increase in mean serum phosphate and magnesium, and a relatively small

increase in mean serum calcium levels.

There was an imbalance not favoring canagliflozin in the incidence of overall fractures and this was also observed in the incidence of upper limb fractures. Canagliflozin was associated with a four to seven-fold increase in the incidence of genital mycotic infections which resulted in an increased use of antifungal therapy; phimosis in male required surgical intervention.

Canagliflozin was associated with an increase in LDL, non-HDL, and HDL cholesterol levels. However, in contrast to placebo, it was not associated with an increase in serum triglyceride levels. And we noted an imbalance in early cardiovascular events, not favoring canagliflozin, in a population of subjects who are at increased risk for cardiovascular events.

I'd like to acknowledge my colleagues and this concludes my presentation.

Canagliflozin: Statistical Assessment of CV Safety

DR. SOUKUP: Good morning. My name is Mat Soukup. I'm a statistical team lead within the

Division of Biometrics 7 in the Office of Biostatistics. What I'll present to you this morning is our statistical assessment of the cardiovascular safety of canagliflozin.

I'll initiate my talk orientating you to the background information into the database that we're going to use in our meta-analysis. This will be covering things such as the trial listing, as well as the patient demographics and baseline characteristics for cardiovascular risk.

Here I have a slide showing the nine trials that are incorporated into the meta-analysis. This consists of Phase II and Phase III trials. The single Phase II trial is trial 2001 which was the smallest trial incorporated into the meta-analysis conducted for the shortest duration of 12 weeks.

The overall sample size is dominated by the one dedicated outcome trial. This is the CANVAS trial listed in top row here. This is a trial that is still ongoing at the time of submission. The majority of the trials are going to be placebo-controlled with two trials incorporating an active control, which is

glimepiride in one trial, and sitagliptin in another.

The data we're using in our meta-analysis, it should be noted is that it is based upon ongoing trials, with the exception of trial 2001, and we're incorporating all data that was available at the time of database lock of January 31st of 2012.

The next slide here, what I show is just to provide a little bit more of a description of the enrolment criteria in canvas. Again, this is a dedicated cardiovascular outcomes trial of which data from a planned interim analysis is incorporated into the trial and that's where get our sample size as shown on the previous slide.

I won't read the specific criteria used in enrollment into CANVAS, but it is to show that this particular trial did enrich the population to enroll subjects with a higher cardiovascular risk at baseline. And this will have downstream effects when we start looking at results by CANVAS versus non-CANVAS trials.

And we can see this even in our most basic summary statistics when we're looking at baseline, and here I'm showing the demographics that shown mean age,

percent that are female, percent for specific rate categories, the mean BMI, as well as percent enrolled in U.S. sites.

I parse this out in two strata that pools the non-CANVAS trials and well as the CANVAS trial on its own. And if you look within either strata in comparing canagliflozin to comparators, we do see a relative balance between these demographic factors. However, when you look at CANVAS versus non-CANVAS trials, this is where you start to see there are differences between CANVAS and the non-CANVAS pooled set of trials.

Specifically, CANVAS enrolled subjects of higher age, as well as a higher proportion that were male, and again CANVAS will done in fewer U.S. sites than the other trials.

Looking at baseline cardiovascular risk factors in a similar way that we did with demographics, we see what we would expect to see in comparing CANVAS to the non-CANVAS trials, as we do see that subjects enrolled in CANVAS do have higher baseline risk for cardiovascular events.

As we would hope, due to the randomization we

do see relative similarities at baseline comparing canagliflozin to the comparators for each of these cardiovascular risk factors.

So next I'll provide a summary of some of the statistical methods that we use. It should be noted that some of the methods that were incorporated were based upon prespecified and agreed upon methods, and we're also going to present some post hoc analyses that we've used, due to the observed data and some challenges that it presented in the statistical analysis.

Overall, the planned objective of the meta-analysis was to rule out a risk margin of 1.8 and this is in line with the cardiovascular guidance as it relates to diabetes products. And this is done by looking at the upper bound of a two-sided 95 confidence interval in comparing it to the 1.8 risk margin.

The primary analysis, as it was defined, is based upon a modified intent-to-treat population defined as all randomized subjects who took at least one dose of the double-blind medication. So with such analysis population in the nine trials we have 6,396

canagliflozin treated subjects and we have 3,327 comparator treated subjects.

The comparison in the prespecified analysis plan was to look at canagliflozin versus all comparators. So the canagliflozin arm pools both the 100 and the 300 milligram doses, and the all comparator arm pools both placebo, glimepiride, and sitagliptin controls. Again to note from previous slide is that majority of these trials were placebo-controlled. So there's only one trial with glimepiride and one trial with sitagliptin.

The composite endpoint used in the meta-analysis is based upon a major adverse cardiovascular event endpoint. The prespecified primary composite is MACE- plus and is shown as this consists of the components of cardiovascular death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina.

As a secondary composite endpoint, we also have MACE and this is our stricter definition that excludes the hospitalization for unstable angina component. In the development program of canagliflozin, all events were prospectively collected

and adjudicated.

In terms of prespecified analysis methods, all methods were based upon time to event methodology and this allows us to calculate hazard ratios and their corresponding 95 percent confidence intervals. The specific modeling procedure used was the COX proportional hazard model with predefined strata of CANVAS and non- CANVAS. So we have two strata.

In addition, there was a planned secondary analysis where we utilized time to event methods in the CANVAS trial alone, and where we looked at time to event method in the non-CANVAS set of trials. In terms of sensitivity analyses that will show is that we did also look at the assessment of proportional hazards as it corresponds to the primary analysis model and this is done through an interaction test, as well as through an examination of the Schoenfeld residuals.

Due to some evidence of the non-proportional hazards assumptions that is apparent in CANVAS as will be shown, we looked at time to event methodology, looking at the first 30 days of CANVAS, as well as time to event methodology in the latter 30 days in CANVAS.

So now I'll provide results of the meta-analysis. The first slide here is to just provide a description of where the events occurred by trial, and we can see there are a total of 201 MACE-plus events that were reported throughout the development program of canagliflozin.

The majority of these did occur in the CANVAS trial, as anticipated, because of the dedicated outcome nature of that trial. In this particular trial, CANVAS did make up approximately 80 percent of all reported events.

So now taking those results and putting that into our COX proportional hazards model, we can observe what our hazard ratios are and provided an estimate of that in the corresponding 95 percent confidence interval, and that's what we show on this slide.

Here we see, based upon this COX proportional hazard model, there's an estimated hazard ratio of 0.91 with a 95 confidence interval of 0.68 to 1.21, and this is looking at the MACE-plus endpoint. We also can look at a strict MACE endpoint and we see results are consistent with the MACE-plus endpoint, with an

estimated hazard ratio of 0.98 and a 95 percent confidence interval, 0.70 to 1.36.

The thing to note here is that the COX proportional hazard model assumes proportionality in the hazards and a violation of this particular assumption can influence our interpretability of such a model, and this will be presented in later slides.

This slide has been shown in several presentations where we breakdown the MACE-plus component or the MACE-plus composite endpoint by each of its components. And as has been shown in other slides, we do see hazard ratio estimates below one for cardiovascular death, fatal and non-fatal MI, as well as hospitalization for unstable angina.

For the fatal and non-fatal stroke, we do see a hazard ratio estimate above one. However, it has a relatively wide confidence interval due to the few events, and this confidence interval does include the null value of one.

This is now providing a little bit of a graphical depiction on the events over time and it's our Kaplan-Meier plot of the MACE-plus events, and

we're looking at all trials here. And what we can see here in this particular plot, we do see the curves for the comparator arm, which is denoted in black, and the canagliflozin arm denoted in red, they are intersecting at two time points in this particular trial; right around 60 days and right around 450 days.

So what this did is it led us to question the proportional hazards assumption. And what we did is we looked at a diagnostic plot to see if that particular assumption of the COX model would hold. And this is what we look at and I'll try to orientate you to what a Schoenfeld residual plot is trying to do.

This, in essence, is a diagnostic plot that we use to determine if any model assumptions hold. Ideally, if proportional hazards would hold, we'd anticipate a blue cloud of points to be centered right around zero. And this we estimate the particular cloud here with the smooth regression line in the dark blue, and if the proportional hazard assumption would hold, we'd anticipate the blue line to be near the red line.

And what we can see here is that particular assumption, or that particular structure in the data

doesn't hold. And that's evident because of several points. The first is this steep early slope, and this is going to be caused by an imbalance in early events which I'll describe in more detail in a couple of slides.

The latter part of the curve, we see after around 450 days, is we see large and wide confidence intervals. This is due to few events observed at this time point, as well as the smaller subject set. However, with the majority of subjects being enrolled or being observed in CANVAS, this particular structure in the data would -- we'd have more information as data accumulates.

So we're going to focus more attention really on the first 30 days and what was going on. Before we did that, we wanted to see, well, where was this non-proportional hazards potentially happening? And what we looked at as specified in the secondary analyses, is we looked at the non-CANVAS set of trials, as well as the CANVAS trials.

So the non-CANVAS trials is shown in the panel on the right here. And several things you can

note that are quite apparent in these particular presentation of the data is we do see that in the non-CANVAS set of trials that there is a consist trend for the comparator curve, survival curve, to be above that of canagliflozin, so suggesting proportionality seems to probably hold in this particular set of trials.

We can also see that the incidence rate in the non-CANVAS trials is much lower than the CANVAS trial, and this is what we would expect due to the enrollment criteria. And it's within CANVAS is where we see this non-proportional hazards likely occurring, as it's due to these early events in the particular model.

So this caused us to now fit separate COX proportional hazards to the data within these strata and specifically breaking the CANVAS trial into two time points looking at the first 30 days, as well as the time point after 30 days. And that's now shown in this slide here.

So if we look at the first 30 days, we do see the 14 events as been described previously, of which 13 occurred on canagliflozin and one on placebo in the

CANVAS trial. Fitting a COX proportional hazard model in this small time frame of data in CANVAS, we have an estimated hazard ratio of 6.49, and we also see a very wide confidence interval corresponding to this point estimate that ranges from 0.85 to 49.64.

When we look beyond 30 days within CANVAS, we do see results that do favor canagliflozin, with a point estimate of 0.89 and a confidence interval of 0.64, with an upper bound of 1.25. In the non-CANVAS set of trials, we do see results that do favor canagliflozin as shown with an estimated hazard ratio of 0.64, and confidence interval 0.34 to 1.19.

So this made us start looking in a little bit further, where were these 13 events on canagliflozin coming from. And this slide shows the subjects that did experience an event within the first 30 days, so we see the 13 events that occurred within canagliflozin specific -- very basic descriptions of the subjects in that trial, as well as the type of event that occurred, and we see the one placebo subject that did experience a MACE-plus event within the first 30 days as well.

And one thing to note here is that there are

seven events that did occur within the first seven days of treatment on canagliflozin. So with this result, what we tried to do is tried to come up with a way to understand why we would maybe be observing the events we did and see if there was any additional sensitivity analyses we could fit to look at the data in a way to understand it.

And what's shown in this slide is a post hoc sensitivity analysis where we're looking at the first 30 days. What we observed in our data was one event as shown. However, if you look at the full set of events throughout the course of treatment in the CANVAS trial and if we would look at any given 30 day time window, we have expected to see about 3.76 events, if we assume there is a constant hazard in the placebo arm.

So what we could have potentially observed in this particular trial is a random low for the placebo-treated arms. So then what we did is in the table below, is we added additional arms to the placebo treatment arm in the first 30 days. So we fixed canagliflozin to the observed rate of 13, and we add additional arms.

So for example, if we add two additional events to the placebo arm in this sensitivity analysis, then we would have three placebo events that would have occurred within the first 30 days. If that's the case, our hazard ratio then would be estimated to be 2.16 with a lower bound of 0.62 and an upper bound of 7.59.

Overall, what this particular analysis is meant to show is, is that it does show that the hazard ratio estimates are very sensitive to only a few events observed in these first 30 days, and it's due to these few events that we're observing in the time frame to draw any definitive conclusions at this time point.

So now I'll summarize our findings. The first is that the prespecified meta-analysis of the MACE-plus composite endpoint resulted in a hazard ratio estimate of 0.91, with a confidence interval of 0.68 to 1.21. This was done by the use of a COX proportional hazards model.

There was some evidence of non-proportional hazards using this particular approach, and it does lead to some questions about the interpretability of this particular model. And this, the reason being is

due to imbalance of early events observed in the CANVAS trial. And as a side note, again proportionately it does seem to hold in the non-CANVAS trials.

So then that really makes us think a little bit more about the secondary and sensitivity analysis of MACE-plus where we look at the non-CANVAS trials on their own and this results in a hazard ratio estimate of 0.64, with confidence interval of 0.34 to 1.19.

If we look at the set of events that occurred after day 30 in the CANVAS trial, we have an estimated hazard ratio of 0.89 with a confidence interval of 0.64 to 1.25. Looking at the first 30 days within CANVAS, we do have a high estimated hazard ratio, 6.49, with the 95 confidence interval 0.85, and an upper bound 49.64.

This is based upon 13 events that were observed among the 2,886 subjects randomized to canagliflozin, seven of which occurred in the first week, and the one event that occurred among the 1,441 subjects randomized to placebo.

And as shown in the sensitivity analysis is that the hazard ratio observed in this portion of the

data is highly sensitive to small changes in the number of events. And lastly, is an acknowledgement to Dr. Eugenio Andraca-Carrera who was the primary statistical reviewer on this application, who gets the credit for the work here and is unable to present his findings. And that concludes my talk. Clarifying Questions from the Committee

DR. THOMAS: Thank you. We'll now take questions from the panel for the FDA. Dr. Knowler?

DR. KNOWLER: Yeah, I'm trying to reconcile this last presentation with an earlier statement from the sponsor which I believe indicated that there was no lack of proportionality. Is that because the two analyses were looking at different datasets, or I'm -- perhaps I misunderstood what was said earlier, but there seemed to be a contradiction.

DR. SOUKUP: We're not saying there's a definite conclusion that there isn't proportional hazards. We're saying there's some evidence. I think it's hard to really detect. The sponsor used an interaction test to assess this, and I think we do have some problems with that being an appropriate test to

make a determination to say that proportional hazards holds.

We think the Schoenfeld residuals are maybe a little bit more effective technique. But it doesn't give you a P-value to say, yes, it's definitely there or not, but we do think there is some --

DR. KNOWLER: But you were analyzing the same datasets. You found the evidence in the CANVAS studies, but not in the other studies. Is that correct?

DR. SOUKUP: That's correct.

DR. KNOWLER: Was the sponsor's statement just regarding CANVAS or all of the studies?

DR. THOMAS: You want to address that?

DR. STEIN: Our statement included -- was looking at CANVAS specifically. I'm sorry, overall. Maybe I'd ask Dr. Capuano just to step up and directly address that.

GEORGE CAPUANO: So the P-values that I presented for those three various tests correspond to the overall CV meta-analysis results, which did include a test of interaction. We also did look at the

Schoenfeld residual plot and you can generate a P-value for the non- zero slope test of the Schoenfeld residuals and that corresponds to a P-value of 0.15.

DR. KNOWLER: Do you think the difference may be simply that Dr. Soukup was analyzing the two sets of studies separately and you're analyzing them all together? Or is there some other reason for what seems like a discrepant conclusion?

GEORGE CAPUANO: I would simply say that the proportionality assumption pertains to the prespecified analysis, both the CANVAS and the non-CANVAS. So taking a look at a various time point cut as opposed to the entire duration is quite different. So based on our assessment, there's the assumption of proportional hazards has not been violated.

DR. THOMAS: Dr. Brittain?

DR. BRITTAIN: Okay. I'm not sure how to interpret the hazard ratio after 30 days, because we don't have comparable groups at 30 days. So I didn't really know -- I mean do you have any help about interpreting that? And my second question is -- it's the same question I asked this morning. Do you have

any data that compares the Kaplan-Meier survival curves because -- at certain points in time in terms of their confidence intervals? The differences, you know, relative risk or differences in event free survival.

The reason I say that is that that would be an alternative way of assessing the difference between the curves that doesn't -- isn't compromised in any way by the lack of proportional hazards. I mean all the -- to me, the only problem with the perhaps lack of proportional hazard is it clouds the interpretation of the hazard ratio estimate. But if you look at separate points in time and you're getting kind of -- you see the same pattern say at six months and 12 months, that would be reassuring to me.

DR. SOUKUP: In terms of the second question, I don't think we've conducted any specific analyses as you've mentioned, but it is something we could look into afterwards. The first question, if you can help me, remind me what --

DR. BRITTAIN: What I'm saying is you're comparing to -- you're saying once you've survived the 30 days, you're now comparing the -- getting the hazard

ratio at 30 days, but you don't have comparable groups anymore because you've lost -- in the treatment group, more people have had events. So you have somewhat incomparable groups at that point.

DR. SOUKUP: Right. You are correct in that. The denominators though -- and I agree, we do lose some of the randomization because of that, but the denominators are very similar at that time point after 30 days at the, at least the initiation of day 30, we do see there are very similar --

DR. BRITTAIN: The denominators are very similar but you've lost 13 to 1 in terms of who's gone out of the population, and that's why, you know, it's -- - to me it's not really clear. You know those groups are not quite comparable.

DR. THOMAS: Did you have a very brief comment related to Dr. Brittain's question?

DR. STEIN: Yes. Slide up. So this was the MACE-plus. Now we don't have it within CANVAS or we could check and see if we do, but this gives the confidence intervals at six and 12 and 18 months by the two treatment groups.

DR. BRITTAIN: That's helpful, but I actually was asking for confidence interval either the, you know, relative risk at each time of comparison. But this is helpful, and I do think it looks fairly favorable for the drug.

DR. THOMAS: So if you have that data, let us know and we could have you show that at the afternoon. Thanks. Dr. Palevsky?

DR. PALEVSKY: So with some trepidation and since I'm not a statistician, it was my understanding that there are other methods besides proportional hazards that can be used in these settings, such as accelerated failure time analysis. Have you tried doing an accelerated failure time analysis for this, which would obviate the concern over proportionality?

DR. SOUKUP: That is something that we have not conducted.

DR. PALEVSKY: Has the sponsor?

DR. THOMAS: Dr. Hiatt?

DR. HIATT: I just wonder if we could get some clarification on the interactions between the FDA and the sponsor on the CV events. So we have 201

events to look at now, but more events are coming. There are questions about excess events early and perhaps later. There's a rise in LDL cholesterol that occurs that might have an adverse effect over time. I'm just curious why we're not looking at complete data. Why are we looking at incomplete data?

DR. SOUKUP: So I guess I don't really -- in terms of complete data you mean?

DR. HIATT: Complete outcome data, complete cardiovascular risk data.

DR. SOUKUP: Well that, I mean the data we're looking at is the data that -- I mean it's the prespecified analysis that was agreed upon. The trial is still ongoing for CANVAS as you heard this morning, however, it's been fully recruited, so the early events -

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DR. HIATT: Won't change.

DR. SOUKUP: -- won't change.

DR. HIATT: And with CANVAS, at least on clintrials.gov -- thank you, Dr. Kaul -- the primary is MACE, not MACE-plus. Did you change your negotiation

with sponsor on how you'd analyze those data?

DR. SOUKUP: I believe the MACE-plus was the prespecified endpoint in the SAP for the meta-analysis.

DR. HIATT: Okay, but that's on the website as it's reported.

DR. SOUKUP: Right. And I can't speak to that. I don't know if the sponsor has additional information on that.

DR. THOMAS: If you have a comment directly related to that question.

DR. STEIN: Just to be clear, when the CANVAS trial was designed, it was originally designed as a CV outcome trial with a benefit endpoint of MACE. It was also designed as part of the CV meta-analysis and prespecified in the CANVAS protocol and in all of our protocols, and in a separate CV statistical analysis plan, that the primary safety endpoint would be MACE-plus for this prespecified CV meta-analysis. So the MACE-plus was prespecified for this CV meta-analysis.

DR. HIATT: So MACE-plus for this interim safety look; MACE for the completion of the trial.

DR. STEIN: Yes.

DR. THOMAS: Dr. Kaul?

DR. KAUL: I'm going to ask the same question I asked the sponsor. I mean can the interim results of a randomized, ongoing clinical trial be used for a preapproval decision and the final results used for a post-approval decision? Yes or no? And I'll ask a follow-up question.

DR. PARKS: So what you're touching on are actually some rather complex issues. When the guidance was issued in December of 2008, after a two-day advisory committee, I don't know if you recall, there were a lot of possibilities raised on how to meet a premarketing threshold to rule out excess risk in the post-marketing? And the intent there was to provide us some reassurance before a drug market gets to market, that it's not overly burdensome, that would delay available therapies that look promising, but then to also allow for us to get ongoing information.

One of the things that as offered was actually to do a two-step approach. And that two-step approach could come from a variety of things, a variety of ways. One of possibilities was to have two

independent sources; so your Phase II and III trials versus an independent cardiovascular outcomes trial.

After the guidance was issued, we did quite a few proposals, and one of the proposals did include interim analyses of a single ongoing trial and that was actually discussed at the advisory committee.

I think issues, and I would have to ask Dr. Soukup to weigh in here, is that when you have reliance on data from a single ongoing trial interim analysis, issues of preserving type one error at -- excluding different margins of risk, concerns about integrity of data because if we're going to be discussing data from an ongoing portion, obviously some -- this information is going to be unblinded to some parties.

So that's certainly some of the concerns that are raised. But the methodology, the technical aspect of whether or not it can be relied on, we could not really identify, at least at this point in time, that a single trial in itself cannot be relied upon to rule out two different risk margins. Mat, I don't know if you want to add anything from a statistical standpoint.

DR. SOUKUP: No, I think that very clearly

covers the issues.

DR. ROSEBRAUGH: Yeah, let me just add something, too. So as Dr. Parks said, you have asked a yes, no question, but it's a very complex issue that does not lead itself to a yes, no answer, readily. And additionally, as we -- as she has indicated, we have a guidance, but little experience with some of that.

So as we accrue knowledge, then sometimes our thinking does change. But also asked -- just the way you asked the question seems to indicate that perhaps you have some thoughts on that. And if you do, then I'd be interested to hear them, because that would help us as we incorporate knowledge that we gain through development programs.

DR. KAUL: I can only speak in terms of generalities. I mean as a general rule, unblinding a trial is not a good thing, okay, unless there are compelling circumstances, and I don't hear those compelling circumstances here. I mean the outcomes trial has already finished enrolment and why not wait for the full dataset before we adjudicate on this? So that's all I can say. And it seems to me, this would

be a precedent setting example.

Are there any precedents where either the EMDAC or any other advisory panel has used an ongoing interim analysis of a clinical trial for a preapproval decision and then the final analysis for a post-approval decision? I mean this is for us. For, I mean I'm not -- but to me, that is the key question before I make up my mind.

DR. PARKS: I actually have a question for you first and then I'll try to answer your question. You said that you had concerns about unblinding the ongoing trial. Is your concern here for the 1.8 or 1.3, because again we're talking about two different risk margins? And then with respect to regulatory precedent and looking at one trial or interim analysis of an ongoing trial, from our standpoint things have come in, whether -- and we have considered this, but nothing in the public domain that can be presented.

So we certainly have accepted this method of excluding different risk margin for cardiovascular risk. I don't know, Dr. Rosebraugh, if you know from other divisions, review divisions if interim analyses

have been used. And obviously the most -- one that you know very well is actually the interim analysis from the RECOR (ph) trial, but that was not for a premarketing --

DR. KAUL: Decision had already been made, but that was just looking at safety issues. So if I take this, if I extend this further, there are two post- approval trials that are going for two diabetes products. If they come back to you with interim analysis having satisfied the 1.3 hazard ratio criteria, would you make it -- will you accept that as a post-approval decision? I'm talking about sitagliptin and liraglutide.

DR. GUETTIER: I mean most of these are time to event trials, so the second analysis is going to be based on a specific number of events, and it's predefined, and it's agreed upon before the sponsor actually performs the analysis.

DR. KAUL: This trial is also an event driven trial, too.

DR. THOMAS: Dr. Rosebraugh, do you have a comment specifically on this?

DR. ROSEBRAUGH: Yeah, I think I just to want to add that I think many of the ongoing preapproval CV outcome trials are in fact based on interim analyses at the time of approval. And I think some of the trials that have been discussed in relation to obesity indications are of a similar design. So I don't think the sponsor today is in a unique position.

I will just also add that, please bear in mind that one of the benefits of doing it this way is that the final exclusion of the 1.3 limit will come that much earlier, because you don't to set up the trial, recruit for the final trial.

DR. THOMAS: Dr. Proschan?

DR. PROSCHAN: So I'm wondering, based on the questions that were asked earlier, whether either side actually computed a P-value for the interaction test for CANVAS. And also related to that same issue, is it -- let's suppose that we accept that there's a difference in the hazard ratio, early versus late. Then at some point you have to figure out, okay, how do I put that all together?

One way of putting that all together is to

compute the COX model estimate, that overall hazard ratio, as that does combine early and late. So is it your contention that that is not a reasonable estimate, a reasonable way to combine both early and late?

DR. SOUKUP: I don't think that's our contention. I think what we're trying to illustrate is ultimately bringing awareness to these first 30 days and we don't know how to make sense of it. It was something, an anomaly in the data that we just didn't quite know how to handle, because beyond that I don't think we had any concerns with the cardiovascular safety.

It's just potential in this first 30 days, and we don't -- we wouldn't say that it's a real finding, but we can't definitively say it's a chance finding either. So I think that's ultimately we're trying to present it in a way to just give you a big picture of what's going on in the data.

DR. PROSCHAN: The other question was whether --

DR. SOUKUP: The P-value. And I'm looking at Dr. Andraca's review here and from what I see in the

review is I only see a P-value for test of all trials combined; so not one separately by CANVAS.

DR. THOMAS: Any other questions, Dr. Proschan? Okay, at this time, we'll now break for lunch. We'll reconvene again in this room in one hour from now at 1:00 p.m. Please take any personal belongings that you may want with you at this time. The ballroom will be secured by FDA staff during the lunch break. Panel members, please remember that there should be no discussion of the meeting during lunch amongst yourselves or with any member of the audience. Thank you. (A lunch recess was taken.) Open Public Hearing Session

DR. THOMAS: Okay. We'll now start the meeting for the afternoon. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open

public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any 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 considerations 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 this open public hearing to be

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

We'll now have open public hearing speaker number one.

KELLY CLOSE: Hi. My name is Kelly Close. I've had diabetes since 1986. It's a big deal to speak here today, and I really thank you for the chance. I'm the editor of three diabetes newsletters. One of the newsletters, Closer Look, is subscription based, and Janssen, along with dozens of other for-profit and non-profit organizations, pay for it. That's the only disclosure I have.

I'd like to emphasize two main points. First, in the U.S., we are nowhere near where we could, and where many experts say we should be, regarding glycemic control, which leads me to ask you to consider broadening our approach to diabetes care.

Second, I believe that canagliflozin is a step in the right direction toward promoting early

glycemic control, with a medicine that is relatively more tolerable, which can increase patient adherence, perhaps significantly.

Adherence, as we've heard, is one of the biggest problems with the diabetes drugs today. And that's not okay, not for any of us. Not for patients, not for doctors, not for nurses, not for payers, not for society, not for citizens.

Given all of the costs associated with diabetes, we can't keep going with this current status quo environment. The most costly one percent of people with diabetes incur expenses of $100,000 a year, according to a 2009 study in pharmacoeconomics. And the most costly one-tenth of one percent have expenses of nearly $1 million a year. So 200 patients costing $100,000 a year is $20 billion. Twenty-thousand patients costing $1 million a year is another $20 billion.

You put these numbers together and you start to see that it's not really the cost of diabetes drugs at $5 or $7 a day that's driving all the spending. The spending is associated with the complications, or bad

outcomes associated with diabetes.

So let's talk about what's at stake. Even with progress in recent years, too many patients are far from optimal control, but half of you, as patients today, do not meet the A1c goal of seven percent, some not insignificant percentages above nine percent.

Virtually no patients are at a normal A1c level. Even, I like to think, that one day, with safe diabetes medications, that will be the real goal for all of us with diabetes, a normal A1c.

We should be able to do better, and I believe strongly that we can with a better, broader range of tools that will help us start to personalize treatment, even just a little bit.

So why are patients still above seven percent, and how canagliflozin help to control? We currently have several powerful drugs for type 2 diabetes. But in reality many patients are failing because most diabetes treatment options come with safety and intolerability issues that really complicate adherence, and that's putting it lightly. We've already heard a lot about that today.

But you know, just to take one class, sulfonylureas are such poor treatment for type 2 diabetes patients that the FDA itself requests that they not be used as comparators in cardiovascular outcomes trials. Yet and still, they're the second most common diabetes medication used today.

But actually, I don't mean to say used, since patients don't often take them, but they are the second most common diabetes medication prescribed today. Maybe given adherence, we shouldn't be surprised by all of these really high costs.

Doctors and other leaders sometimes talk about how great it is that we have drugs that work for diabetes. So we don't need more drugs that work, we have drugs that work. We need more drugs that patients will take, and take consistently, and we need more education.

Canagliflozin is a new class of drug with a new mechanism, and that's a really big deal. If approved, canagliflozin would offer a valuable alternative, especially for patients who have difficulty tolerating current options.

It has a low risk of hypoglycemia. And the most common side effect, genital urinary infections, would certainly be inconvenient to treat and to have, but on the continuum of tolerability issues, it is on the less severe side.

Beyond the drug's relative absence of unfavorable side effects, canagliflozin also has demonstrated numerous benefits beyond its robust A1c reduction. We've already gone through a lot of that today.

So notably, given that it's an oral drug, and given its positive tolerability profile, especially relatively speaking, canagliflozin could be used earlier in disease progression than most ingestible drugs, and less tolerable oral drugs.

That leads to two big benefits. First, greater adherence could delay patient's disease progression. Second, it could delay or prevent the development of complications.

And it's an old line, but diabetes patients are living longer; delaying or preventing complications is increasingly important. We all know

that this is especially true given the financial stress on our healthcare system.

Finally, as I've alluded to, canagliflozin could be valuable for healthcare providers. Anything that's valuable for doctors and nurses is great in my book, especially because we all want to keep them as excited as possible about doing their job, especially given the shortage of healthcare providers; especially the shortage of healthcare providers that are treating diabetes today and that want to treat diabetes, and that are going into this field.

Primary care doctors, in particular, need safe, effective, easy to prescribe, and easy to use diabetes drugs that will work in a broad range of patients. And effective and lower hassle, even if it's not hassle free, agents such as canagliflozin, can counteract the clinical inertia that often delays the introduction of a much needed third tier or fourth tier medication.

So to conclude, canagliflozin has the potential to bring more patients to goal, to promote early glycemic control, and to become a practical and

thereby valuable agent for both patients and healthcare providers. There's some safety concerns. It sounds like they can be addressed. And it doesn't sound like these come close to offsetting the drug's benefits.

Given the need to improve diabetes care, and the promise of canagliflozin in this new class, I ask for your careful consideration and ask you to vote in favor of its approval. The current status quo is not working and you hold the future for diabetes patients in your hands. Thank you.

DR. THOMAS: Thank you for your comments. We'll now move to open public hearing speaker number two.

GEORGE GRUNBERGER: Thank you, Dr. Thomas. I'm George Grunberger. I represent the American Association of Clinical Endocrinologists, the world's largest organization of clinical endocrinologists. I was an investigator of one of the early Phase III trials of canagliflozin, but I have no financial ties to the company.

We already heard about the burdens of type 2 diabetes, and Dr. Horton and Dr. Gerich and others have

already told us how many people with type 2 diabetes we have. The burden is growing. We heard about economic costs of the disease. And we should emphasize that, as of today, more than a quarter of Medicare recipients have diabetes, and about a third of the entire budget of Medicare is spent on diabetes.

We heard about it's the leading cause of blindness in adults, kidney failure, lower limb amputations, and we heard about the other horrible complications and morbidity and mortality of patients with diabetes. We also heard that the control of type 2 diabetes remains suboptimal, even though we have tools available to us.

Now we cannot cure diabetes today yet, but controlling glucose levels can hopefully do something about the long-term complications, but you already heard that we're not doing a great job, and probably fewer than 50 percent of all patients with type 2 diabetes, under treatment, are actually achieving their glycemic targets.

And the barriers, obviously, as you heard, are many. But two most commonly mentioned are the ones

which you already heard about, the fear of hypoglycemia and fear of weight gain. The large studies of type 2 diabetes, such as ACCORD, ADVANCE, VADT, showed that intensively treated patients, the risk of severe hypoglycemia went up two to three times, and people fear hypoglycemia. In this particular study, patients feared severe hypoglycemia as much as they would going blind.

Now, these episodes unfortunately very often are not recognized. And having today the ability to do continuous glucose monitoring, you can see that both the patients with type 1 and type 2 diabetes, these episodes are very common, and they're not recognized very commonly.

In one study, 74 percent of these events actually occurred at night. And in another study, more than half of these hypoglycemic episodes were nocturnal, and none of them were detected.

Now why should anybody care about that? In this particular study, it was just published in Diabetes Care 2011, the large retrospective study showed that the patients who did experience acute

hypoglycemic event also were far more likely to suffer an acute cardiovascular event. And as you know, cardiovascular events are the leading cause of death in patients with type 2 diabetes.

So the patients suffered the consequences of hypoglycemic events, as far as reduced wellbeing, reduced productivity and increased treatment cost. There's no question about it.

The other side of that, of course, is the weight gain and the epidemic of obesity we're facing today, of both the type 2 diabetes and obesity. As you know, the majority of patients, people in this country are overweight or obese.

Certainly the vast majority of patients with type 2 diabetes are obese or overweight. And we know about serious medical problems are consequences of obesity which are affecting every younger age group in this country, which leads again to more increases in healthcare costs.

So we have issues, and the question is what are we going to do in the future? The American Association of Clinical Endocrinologists has issued

many white papers, task force reports, guidelines and algorithms, and trying to help practitioners to manage patients with type 2 diabetes to achieve glycemic control hopefully more safely, and we try to emphasize treatment approaches which will again try to reduce, or minimize, or eliminate the risk of hypoglycemia and weight gain, if possible.

The second part, which you cannot see very well on this slide, but you can access on the website, aac.com, tries to have both the practitioners and the patients choose the drugs which are listed along the horizontal side. As far as the benefits and risks, try to see what can you do in a particular situation to hopefully achieve glycemic control, trying to maximize benefits and minimize risks.

And of course it's a challenge because we do not advocate approval for any specific drug, but we'd like to emphasize the principles. There's a great need for new drugs to help manage the ever increasing burden of type 2 diabetes, and we certainly need more effective medications to improve glycemic control for our patients with diabetes, without those risks of

hypoglycemia and weight gain. Thank you very much.

DR. THOMAS: Thank you for your comments. We'll move to open public hearing speaker number three please.

PAULINA DUKER: Good afternoon. I'm Paulina Duker, an advanced practice nurse and a certified diabetes educator, serving as the Vice President of Diabetes Education and Clinical Programs at the American Diabetes Association. The ADA represents 15,000 professional members, and nearly 26 million Americans with diabetes. I have no conflicts, financial or otherwise.

Although the ADA does not testify in support of individual products, the association strongly supports the need for further research and improved therapies for the treatment of diabetes as an unmet need. Studies, such as the UKPDS and the Kumamoto study have demonstrated as much as a 40 percent reduction in severe eye disease, kidney disease and nerve complications for every one percent reduction in hemoglobin A1c. However, diabetes remains the most common cause of blindness in working age adults, and

the most common cause of end stage renal disease in the U.S.

Although the CDC have reported improving trends in hemoglobin A1c since 1999, over 40 percent of individuals with diabetes continue to have values in excess of seven percent, the standard benchmark of diabetes control for most patients. Treatment complexity and side effects, together with limited therapeutic agents contribute to our inability to achieve treatment goals.

Traditional therapies, such as sulfonylureas and insulin, aggravate already problematic weight problems that most people with type 2 diabetes are trying to deal with. The ideal diabetes therapy would be one that is easy to take by mouth, with little or no risk for hypoglycemia, no associated weight gain, and a favorable side effect profile.

The ADA, and the European Association for the Study of Diabetes, assembled a work group which produced the joint ADA/EASD treatment guidelines for type 2 diabetes in June of 2012. The guidelines clearly delineate individualized treatment targets for

patients, depending upon the individual's life expectancy, disease duration, established comorbidities, risk for hypoglycemia, resources and support systems, as well as capacity for self-management.

For healthy adults, a reasonable glycemic goal might be the lowest A1c that does not cause severe hypoglycemia or weight gain, using agents and treatment regimens that are relatively easy to adhere to. Hypoglycemia has long been identified as the limiting factor in the treatment of hypoglycemia associated with diabetes.

A recent work group defines iatrogenic hypoglycemia as all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm. A single threshold value for plasma glucose concentration that defines hypoglycemia cannot be assigned because glycemic threshold for symptoms of hypoglycemia shift to lower plasma glucose concentrations after recent episodes of low blood sugar, and to higher plasma glucose concentrations in patients with poorly controlled diabetes and infrequent

hypoglycemia.

Because type 2 diabetes is more prevalent than type 1 diabetes, most episodes of hypoglycemia, including severe hypoglycemia, occur in people with type 2 diabetes. There's growing evidence that patients with type 2 diabetes might be particularly vulnerable to adverse events associated with hypoglycemia.

Over the last decade, several large trials examined the effect of glucose lowering on cardiovascular events in patients with type 2 diabetes, three of which you've heard about. A total of 24,000 patients with high cardiovascular risk were randomized to either intensive glycemic control or standard therapy.

In the studies, subjects randomized to the intensive arm experienced more episodes of hypoglycemia than those randomized to the standard treatment arm. All the trials clearly demonstrated that an episode of severe hypoglycemia was associated with an increased risk of subsequent mortality.

Obesity is a national epidemic, with the CDC,

the Centers for Disease Control and Prevention, finding that over 35 percent of American adults is obese. Obesity both increases the risk of developing type 2 diabetes and exacerbates its treatment and complications. With increasing weight comes progressive insulin resistance.

Of the primary therapies for type 2 diabetes, metformin, sulfonylureas, and insulin, only metformin is weight neutral, with both sulfonylureas and insulin resulting in significant weight gain. Although these drugs are generally safe and reasonably effective, individually and collectively they do not come close to providing the complete treatment armament for type 2 diabetes.

The American Diabetes Association strives to improve the lives of individuals with diabetes. Promoting glycemic control to minimize the risk of microvascular complications must be tempered with minimizing the risk for hypoglycemia, weight gain and other drug-induced side effects.

We have moved to a more patient-centered approach to diabetes treatment with our most recent

guidelines. This requires the availability of a broad spectrum of treatment modalities to meet the needs of the almost 24 million Americans affected by type 2 diabetes. Thank you.

DR. THOMAS: Thank you for your comments. We'll now move to open public hearing speaker number four.

SIDNEY WOLFE: I'm Sid Wolfe. I do not have any conflicts of interest. Thank you. Can you turn the lights down a little bit please? Is it possible just to -- these are just some things that we can all agree with, as opposed to differences of opinion.

The approval request is based solely on surrogate efficacy of HbA1c lowering. As with all recently approved type 2 diabetes drugs, no evidence of any improved clinical outcomes, contrary to an older diabetes drug such as metformin, and the question obviously is this surrogate efficacy of canagliflozin needs to be balanced against a number of serious clinical safety signals identified in the clinical trials.

This is on dapagliflozin, but you'll see in a

minute why I looked at it because it looks like the osmotic diuresis that occurs with this drug is much more serious than with dapagliflozin. These are studies that were presented at a meeting on this drug. And five events, for 0.4 percent, versus 24 events related to volume depletion, not statistically significant.

On the other hand, when you look at the data on canagliflozin, in just 30 days, again this same first 30 days where a number of other problems have arisen, there was one event in the placebo group, for 0.3 percent, and 16 in the canagliflozin group for 2.3, and that obviously was highly statistically significant.

Several times, in both the presentations it has been mentioned, this early cardiovascular event increased 13 events in the canagliflozin group, one in the placebo group. And it does coincide with the same period of time, the first 30 days, where there is a significantly increased amount of volume depletion events.

Part of volume depletion can include

hemoconcentration. And what I did here is take the data from dapagliflozin and compare it to the data we now have on canagliflozin. And this is the absolute increase in hematocrit, so 1.57 would be from 45 to 46.7 (indiscernible). And what you can see is that there is much more of an increase in hematocrit in the people getting canagliflozin, 1.5 times as much as the dapa group in both doses. It's a little bit lower in the high dose.

The point of this is, is this is drug-induced hemoconcentration. And it is well known that when you get into these high ranges of hematocrit, there's an increased risk of thrombotic events. And most of what is going on here, in terms or cardiovascular risk, is increased thrombotic events.

The data were available for dapa in terms of the breakdown of the percentiles and the mean. And if you project those, they're going to be worse in the canagliflozin. We're talking about a quarter of the people on this drug having hematocrits above 47. So we're in a very dangerous range, which would be treatable if you were looking at people with

polycythemia vera or any other source of polycythemia.

And this you've seen before, this is again the MACE breakdown. And it's simply to point out, which has been pointed out in a different way by other people, that although the overall MACE ratio was 0.91, the largest component of it was stroke, and it was almost all thrombotic stroke, if I remember correctly from this morning.

And it had a 1.46, not statistically significant, but the upper bound was 2.58, and that is above the 1.8 that was specified for cardiovascular risk. Now, it's been interpreted to mean just the MACE here, but it obviously is of concern.

These are just comments from the FDA briefing book on renal function. With moderate renal function, the early drop in GFR appears to persist over time. I'll skip this because it's been covered very nicely by the FDA in terms of renal problems.

This is an answer from a consult that the FDA sought from the renal division. The applicant has not provided data that speak to the long-term renal consequences of extended exposure to the drug in the

proposed population. And then further, the renal consult talked about other kinds of problems, safety, long-term decrease in GFR.

And finally, we just get to the summary of the benefit risk. Dr. Hiatt asked the question this morning whether you're doing more harm than good if you lower the blood pressure in the way that it's done with this drug.

I think the larger question is, are we doing more harm than good by lowering hemoglobin A1c with all of the different problems that seem to be clearly occurring. For a drug that offers a new mechanism of hemoglobin A1c lowering, devoid of any evidence of clinical benefit, the list, and I've only given a partial list here of the serious concerns, argue strongly against approval.

Short-term and long-term risk to renal function related to hypovolemia and dehydration in the elderly and those patients on diuretic and/or hypertensive therapy. Again, I repeat the significant problem of hemoconcentration. The extremely troublesome early 30- day increase in cardiovascular

events and in an enriched population is something that Dr. Kaul had asked for a year-and-a-half ago when the other drug in this family was being looked at, coincident with an early 30-day significant volume depletion. And finally, the unknown long-term effect of increased urinary infections and general infections on renal function and reproduction. Thank you.

DR. THOMAS: Thank you for your comments. We'll now move to open public hearing speaker number five.

BENNETT DUNLAP: Good afternoon. Thank you for this opportunity to comment on diabetes medications. My name is Bennett Dunlap. I'm an ePatient advocate and write the blog Your Diabetes May Vary. I have a Master's degree in health communications that certainly didn't prepare me to pronounce things like canagliflozin. I have no relationship with the sponsor.

A portion of my gas and tolls today is being paid by the Diabetes Advocates, an association of patients and social media writers. We see social media as an important way for patients to become informed

about options to consider with their healthcare professionals.

Four years ago my primary care physician told me I had elevated fasting glucose levels. As Kelly mentioned, there's not enough endocrinologists and specialists, and it took me a half a year to get an appointment to confirm that I was in fact type 2, which wasn't a really big surprise because I have a father and sister who are type 2, and two of my kids are type 1.

My father and sister have been the beneficiaries, and I have been the beneficiary, of different care plans for our respective type 2 diabetes, each tailored to our individual situations. And I'm confident that just as my family care varies, so do the needs of other individuals in the population of diabetes patients in the United States. So I'm pleased to see that the drug under consideration today was studied with a wide range of individuals. Like other options, it may be a better choice for some patients than others.

I love Kelly's comments, when she said that

we need type 2 drug options that people take, and that work. Each of us deserves the opportunity to work with our healthcare professionals to find the mix of medications, that in combination with lifestyle changes, successfully helps us manage blood sugar levels. Many of us may benefit from, even if we cannot pronounce, canagliflozin. And I got closer that time.

This class of medication offers an exciting opportunity for a new means of glucose control. Significantly, as has been said, there's a reported mix, or a reported lower level of hypoglycemia. Dr. Grunberger and Ms. Duker made it very clear that hypoglycemia matters. Fear of hypos is a deterrent to compliance, even for those of us that should know better. I found it significant this morning to hear that one of the medical professionals involved with the studies had that experience themselves.

SLG2 (sic) therapies may offer something beyond medication to improve glucose levels without increasing the fear of lows. They may offer health practitioners a small piece of art that may be akin to magic for some of us patients.

Type 2 diabetes is invisible. I certainly had no symptoms, but my blood sugars were spinning out of control. Also, progress towards successfully managing diabetes is just as difficult to perceive. I often feel that medical literature, with possibly the exception of my friend from AACE -- did I get it right -- projected diabetes care as easy and that results are the straightforward implications of switching on something called compliance.

I know that I and other patients have felt frustration when we have found the process to be very difficult. Even more so, when the lack of expected results is seen by providers as a failure of compliance and effort on our part when some of the treatments we have been given have known side effects to thwart those very expectations.

For some the next few pounds are harder to lose than previous 30. The next half point of A1c is harder to achieve than the first, despite taking good care and doing what we've been prescribed.

The lack of symptoms in type 2 diabetes makes it easy for patients like myself to spin out of

control. Diabetes self-care is not easy, particularly when what patients see from treatments is weight gain and frightening lows.

This medication may be a tool physicians can use to help stop some patients from spinning out of control. It may help us see emotionally tangible results that, without hypos, that promote healthy lives. And for those healthier lives, I thank you all.

DR. THOMAS: Thank you for your comments. And I also too have trouble with many of the names that come before this committee as well, so you're not alone.

The open public hearing portion of this meeting has now concluded and we'll no longer take comments from the audience. Questions to the Committee/Committee Discussions

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

We do have a list of names from this morning that did not get a chance to ask questions, so we'll

use that. And also, if you have a question that you'd like to ask, please raise your hands and we can add you to the list.

But before we get started, Dr. Brittain had asked the sponsor if they were able to provide some additional data and I was wondering if you were able to obtain that or not. Yeah, I think that was correct, right? If you have it, if not, that's fine. Okay, well just give us a signal when you have that. Dr. Gregg?

DR. GREGG: Sure. So these are remnants from this morning, but I actually had two separate questions. The first is that given the large blood pressure reductions that were seen, apparently through a different mechanism than ordinary, I'm wondering whether, in these trials, whether there's any attempt to examine how the profile of concomitant treatments changed over time, over that two years.

Specifically whether there's compensation in terms of the prescription of other drugs, potentially protective, that happened in response to those blood pressures. So more specifically, I'm wondering whether

the medication changed over time.

The second question is really unrelated to that, but it has to do with the characteristics of the populations in all these studies, which on the whole appear relatively representative. But the sort of glowing exception of that is that there's only two or three percent, maybe four percent African-Americans in these studies.

And this is, you know nationally, this is 15 or 20 percent of the population, really even more if we were to think about the target population for this drug. And I'm curious as to whether in the meta-analysis, or the pooled analysis, you're able to look at that subgroup.

DR. STEIN: With regard to changes in medication over time, I think perhaps one medication which might be considered as a likely change would be ACE and ARB therapy since it's the most common anti-hypertensive therapy.

If I could have the slide up, slide up. So what we looked at here are subjects who had ACE or ARB therapy at baseline. This is from our broad dataset,

so this is over about 16 months of average duration of exposure.

And I think you can see that, first of all, that about two-thirds of our subjects were on an ACE or ARB at baseline. And then the change in that was relatively minimal. There was a small reduction in the use of ACE or ARB therapy that was not particularly different across the treatment groups.

On the other hand, if you look at diuretics, slide up, a similar type of observation. Again, the top row looks at the proportion of individuals, again from our broad dataset, who were on diuretics at baseline.

And you can see perhaps a slight reduction with canagliflozin, but a reduction also in the non-canagliflozin group. So I think the conclusion we came to was there wasn't a dramatic modification of the concomitant medication regimens.

You asked about the information in the African- American population. We have looked both at the pharmacokinetic, pharmacodynamic efficacy and safety responses and I can comment through those, just

briefly, if I may.

So with regard to the pharmacokinetic exposure, it doesn't appear to be any meaningfully different by ethnic groups, and in particular not different in individuals who are African-American.

In regards to the pharmacodynamics response, I'll say that we have relatively limited information in the small numbers that we have pharmacodynamics information, and here I'm referring to the endpoint which we were using, which was the renal threshold for glucose.

Canagliflozin lowers that threshold and we looked at that in individuals with different ethnic and racial backgrounds and really didn't notice very much differences at all, which I think we anticipate since the expected effect of the level of kidney would likely be similar.

We've also looked at efficacy across different ethnic groups. And maybe I'll ask Dr. Meininger just to comment just very briefly on the efficacy, and then we can also show you some safety data in African-American subjects.

GARY MEININGER: Right. So just to remind you, across the Phase III program, we enrolled approximately 450 subjects. Again, the majority of black or African- American subjects came from the United States, and of the proportion that we recruited, represented about 14 percent, so consistent with the proportion that you were quoting in terms of the United States.

Slide up. In terms of efficacy, I showed this slide earlier in terms of the subgroup analysis. And if you turn your attention to the third grouping of race, you can see that there was no interaction of race with being white, black or African-American, Asian or other, both for the canagliflozin 100 milligram dose as well as for the canagliflozin 300 milligram dose.

DR. STEIN: Thanks, Gary. Slide up, and then just very briefly with regard to safety. This is the experience, again, in our broad dataset, and you can see that we had a moderate number of individuals in this dataset that were black or African-American.

As you can see, the overall incidence of adverse events, not notably different, slightly higher

at 100, not notably different at 300; adverse events leading to discontinuation, serious adverse events, and deaths not notably different; adverse events related to study drug modestly increased, as we've seen across our program. Those are largely the genital mycotic infections and the polyuria, polydipsia, thirst that account for those differences.

And so this profile is quite similar to what we've seen across the broad dataset. So our conclusion was that PK pharmacodynamic response, the efficacy response, and the safety profile don't appear to be meaningfully different.

DR. THOMAS: Thank you. Ms. Killion? Dr. Guettier?

DR. GUETTIER: I think the sponsor also provided data on the discontinuation rate for patients who were on metformin at baseline and maybe that is something that would be useful to see.

DR. STEIN: On metformin at baseline?

DR. THOMAS: Is that by racial group or just --

DR. GUETTIER: I recall seeing, in the NDA, a

figure which showed the rate of discontinuation of metformin patients with moderate renal impairment, I believe.

DR. STEIN: I mean in our studies of moderate renal impairment, we excluded the use of metformin since it's not indicated in that. So I'm not exactly sure which slide you're referring to. We do have a discontinuation rate across the whole program which I can show. Is that what you're looking for?

DR. GUETTIER: We were looking for discontinuation rate specifically for anti-diabetics, in DS1.

DR. STEIN: We'll see if we can find that. I'm not exactly sure.

DR. THOMAS: Okay. Maybe when you -- let me know when you have that.

DR. STEIN: Yeah. And if you can provide the reference to the specific table, I'm sure we'll have a slide of it. But I'm not exactly sure what you're referring to.

DR. THOMAS: Ms. Killion?

MS. KILLION: I have a question that relates to the incidence of genital mycotic infections and UTI. One of my concerns, as you're heard expressed in the open public hearing, is barriers to adherence. So I'm a little bit concerned about this and I'd like a little bit of information clarifying from the sponsor.

Can you clarify for me if the incidences of these kind of infections were seen more at the initiation of treatment and dissipated over time? Or whether there was something that was likely to recur while you were on this therapy?

DR. STEIN: If I could have the slide up. And what I'll start with is female genital mycotic infections, and if you like I'd be happy to provide similar information with regard to the male genital mycotic infections.

So this is the Kaplan-Meier for time to event for the female genital mycotic infections. And as you can see, in terms of at least the accrual of patients with first events, what we've seen is that the curve begins to flatten at around 26 weeks, and then after 52 weeks it's further flattening, so the accrual of

additional events appears to be decreasing.

With I think the caveat here that the numbers of subjects, as you go beyond 52 weeks, begins to decrease. And so the estimates around this I think have to be taken into -- the confidence around these estimates would have to be taken into account.

If I could, I'll show this similar picture for the male genital mycotic infections, slide up. So the pattern here, we saw some slight differences by dose. But as you can see, here there's a little bit more of an increase through 52 weeks, but again with what appears to be a plateau, and once again with the caveat that the numbers after week 52 are a little bit more limited.

And you asked about recurrence rate, and we can show you some information that we have about recurrence rate as well. If I could 564 please. Thanks. So I'll start with the recurrence rate that we saw in males, slide up. So this is individuals -- and again this is in our broad dataset, and just to again orient you, this is about a 16-month average duration of exposure, and about three-quarters or more of the

subjects who've had at least a year of exposure.

The incidence in that dataset, I think I presented this data earlier, in the top row, as you can see, the increased incidence with canagliflozin, both doses, and then looking at the numbers of subjects who have more than one event in the second row.

So overall in the population, about 1.6 percent at canagliflozin 100, 2.7 percent, or 2.1 percent overall with more than one event of a genital mycotic infection.

And then slide up, so this is the same information for female genital mycotic infections. And again, the top row is data that I had previously showed with regard to the incidence of these in this broad dataset. And then you can see that overall about 4.6 percent of women had more than one of these adverse events.

DR. THOMAS: Dr. Nakela Cook?

DR. COOK: Thank you. I actually would like to ask the sponsor a little bit more about the hazard ratio for stroke in the studies here. I guess my concern is that it's hard for me to draw a conclusion

as to why we may be seeing this increased hazard ratio that's in the non-significant range.

And I know that we went through several reasons that the sponsor kind of investigated. But I guess I wonder if the look at this data being interim may not just provide us with enough events in order to really understand whether or not this may represent true harm. And I wondered if you could speak a little bit to that, as well as what you think the potential mechanism would be if this is truly related to harm.

DR. STEIN: Well as I commented earlier, I think our primary assessment is that the composite endpoint would be the most robust because of the number of events. And I think in that composite we had a reasonably sizeable number of events, 200 events. And the number of events within each of the elements of the composite being smaller, we expected to see more variability. Three of the hazard ratios, as I noted, were below one, and one was above one, the hazard ratio for stroke.

I will note that we did look to see whether there was any evidence of an exaggerated diuretic

response, greater hemoconcentration in individuals with stroke compared to those who did not have a stroke. We didn't notice any meaningful differences. We also looked to see whether there was a greater reduction in blood pressure, didn't notice any differences in blood pressure as well.

We looked to see whether there was an overlap with these events that we've been discussing of reduced intravascular volume-related adverse events that might reflect dehydration, and we didn't see any meaningful overlap. There were three individuals who, out of the 47, who had a stroke, who had one of these adverse events.

I commented that the time courses also appeared to be different, and maybe if we could show the Kaplan- Meier for -- thank you, slide up -- for stroke. This, as you can see, appears to particularly separate at about week 18. And I won't show this again, but I did comment previously that when you look at the time to event Kaplan-Meier curves for the reduced intravascular volume- related adverse events, those rise, again as we discussed, rather early on,

with a peak at around 18, and certainly by 26 weeks there doesn't appear to be accrual of additional events. So the Kaplan-Meiers appear to be quite separate.

I commented that the dose dependency was very evident for the reduced intravascular volume of the adverse events, but strokes were actually quite the same in both the 100 and the 300 milligram group.

Finally, I think the other point that is worth making is that if one was to expect to see dehydration, volume depletion, leading to events that reflected the hypercoagulable state that that would induce, one would expect to see that to be generalized.

You'd expect to see an increase in venous thromboembolic phenomenon, which we have not seen any notable imbalance. And we would have expected to see this in other arterial beds.

And as I commented before, myocardial infarction and the unstable angina are both events reflecting a thrombotic diatheses. Both had hazard ratios less than one. So I think our assessment of this is that it most likely reflects the play of

chance, as again this difference is not a statistically significant difference.

DR. THOMAS: Dr. Kaul, you wanted to follow up and then we can --

DR. KAUL: Yeah. Have you done the breakdown on the type of stroke, the ischemic versus the hemorrhagic or undefined? Because we saw the data presented by the FDA, 37 versus nine ischemic stroke. They did not show the hazard ratio. Did you do the analysis to see whether it was significant or not?

DR. STEIN: I don't know if we have the hazard ratio for specifically ischemic strokes. Slide up. I can again show the distribution of strokes that we saw, ischemic, hemorrhagic, undetermined. As you can see, the top table shows across the entire CV meta-analysis population.

The bottom is the CANVAS study information to show you the types of strokes. It was, as typical, a predominant of ischemic strokes, but again some hemorrhagic and undetermined types of strokes as well.

DR. KAUL: I mean it stands out in the CANVAS trial, in the non-CANVAS dataset, and even in the

extended phase of the data through November 2012 when you have 271 events, and I'm kind of curious about this.

This is a lingering concern and whether it's statistically significant or not is not that big of an issue, but if you look at the 37 versus nine, I just did a rough back of the envelope analysis and it excludes a hazard ratio of one. So for whatever that is worth.

DR. STEIN: Well as you commented, and as was provided in the briefing book, there was another analysis done, as requested by the European Medicine Agency. They asked us to update the information on stroke. We provided the update in the briefing book.

The information's only recently been submitted to the FDA, so I won't go into any details. But just to say, slide up, that, as you point out, the updated analysis showed that with now another approximately 80 overall MACE plus events, and I think this is an additional 20 strokes, the hazard ratio, the original is shown here, 1.47, now the hazard ratio of 1.29. So I think that's consistent, from our

assessment, that the initial hazard ratio of 1.47 well could still reflect the play of chance.

One other point I think probably worth making is that, as I commented before, I think you'd expect if you were going to see an increase in ischemic strokes, you would also see an imbalance in transient ischemic attacks. And as I noted before, the hazard ratio for the transient ischemic attacks, slide up, and again the number of events are not large, but the hazard ratio for transient ischemic attacks shows complete balance.

And I think in most studies where there has been imbalances in strokes, and in studies where there's been increases, it tends to parallel with more transient ischemic attacks. In fact often, particularly in situations of hypercoagulability, one also sees increased venous thromboembolic phenomenon. All we've seen is the one event of stroke being increased, again in non- statistically significant fashion, with these other types of events not increased.

DR. KAUL: Two quick follow-up. Have you done an analysis where you've combined TIA with stroke,

number one? And number two, I asked you earlier in the morning, do we have any idea about what was the impact of these strokes on patients? In other words, were they disabling or not?

DR. THOMAS: And before you answer, can I ask the sponsor to be more succinct just because of time issues? Thank you.

DR. STEIN: Certainly. We don't have follow-up -- we don't have an assessment by disability. We have not done a pooled analysis with TIAs and stroke.

DR. THOMAS: Dr. Hiatt, you had a follow up on that?

DR. HIATT: I don't want to add too much to this, but it is notable that of the early MACE events on drug, five of 12 were strokes. The other thing that I find notable is that most cardiovascular trials, a composite of MI, stroke or death is dominated by fatal and non-fatal myocardial infarction. And so the number of strokes, for whatever reason, seem to be inordinately high in this cardiovascular outcome trial. Yeah.

DR. THOMAS: Dr. Malarkey?

DR. STEIN: I might just comment that when we look at other cardiovascular outcome trials, looking at the incidence of stroke, the incidence we see doesn't appear to be notably different. I perhaps can show some data across the literature. Again, I'm not showing this to --

DR. THOMAS: I think we're going to go into the next question. Dr. Malarkey?

DR. STEIN: Okay. Sure.

DR. MALARKEY: Thank you. My comments and questions are in regard to the two-year animal studies. This was presented in the FDA briefing. There's an interesting assortment of neoplasms, clearly increase in incidents, and that includes renal tubular adenomas and carcinomas, pheochromocytoma, and Leydig cell tumor of the testis. And there appears to be class effects in other similar chemical, similar drugs. You see it in the mice and rats as well.

So I'm wondering about the target for this drug, is the kidney, and it's the site of these lesions as well. And a kidney lesion might be related to a pheochromocytoma. So my question is, was there

exacerbation of a nephropathy in the kidney that might have been related to the kidney tumors or the pheochromocytoma? And was elevated LH found in this study for the Leydig cell tumors?

DR. STEIN: So I'll just make a very quick comment and then I'm going to actually as Dr. Cohen, who has helped us with a number of the investigations that we performed, to summarize some of the information.

Just as a quick lead in, what I comment to say is that we've done an extensive mechanistic toxicology program, which I think has demonstrated that the findings relate to carbohydrate malabsorption that we see in rats that we don't see in humans.

In answer to your question about LH, yes LH was increased in rats and we've looked at that in our clinical studies from archive specimens, and canagliflozin does not increase LH in the clinical setting. Dr. Cohen?

SAMUEL COHEN: Sam Cohen, University of Nebraska Medical Center. Dr. Stein has adequately I think addressed the Leydig cell tumor. The renal cell

tumor, just to begin with, there was no impact on the nephropathy that would explain the renal tumors. If I could have a slide up please? CANA is a selective SGLT2 inhibitor, but it does have some SGLT1 activity when it is high enough concentration in the GI tract.

And this leads to some inhibition of the transport of glucose, leading to a malabsorption with its sequelae of increased pH in the GI tract -- decreased pH in the GI tract and increased calcium absorption, urinary excretion of calcium.

This is also associated with tubular injury in the kidney that is indicated by Kim-1 and by histopathology. And there is an increase in cell proliferation as evident by BrdU labeling. The key is that this can be -- these effects can all be inhibited when you inhibit this malabsorption by giving a fructose- based diet instead of essentially a glucose and lactose- free diet.

This is similar to what had been previously reported 15, 20 years ago with the carbos, which is a glucosidase inhibitor and has the same effects on the carbohydrate malabsorption, with the same associated

effects, not only kidney tumors but in pheochromocytomas.

And then in the humans, there's no evidence that you're getting this malabsorption effect so that I think that there would be no implications with regard to human relevance of any of these tumors. Similarly, with the adrenal tumors, the increase in proliferation occurs when you're on CANA on a regular diet, and as soon as you substitute the fructose, that goes away.

DR. MALARKEY: Can I follow up? I appreciate the excellent mechanistic studies that were performed and agree that it's different in humans than the rodents. One follow-up question was do they have pituitary tumors?

SAMUEL COHEN: As far as I know, there were no increase or decrease in pituitary tumors.

DR. MALARKEY: Okay. Thank you.

DR. THOMAS: Dr. Proschan?

DR. PROSCHAN: Yeah, I think one of the problems I think, with just looking at these raw numbers like you see 13 to 1, you know 13 in the drug group and 1 in the placebo group, is, you know we're

not taking into account in our minds the fact that this is 2 to 1. And so you don't expect 7 to 7, you expect something more like 9 to 5, or 10 to 4. So 13 to 1 sounds dramatic, but not when you think -- you know, it's not as dramatic when you think about the fact that it's a 2 to 1 randomization.

The same comment with the 37 and 9. You know, that's 46 events. You don't expect 23 of them to be in each arm. You expect something like a 30 to 15 split, or a 31 to 14 split, 30 to 16 or 31 to 15 split. So I think we have to keep that in mind.

The other thing -- and I'm actually, I'm making comments, I don't have questions, and is this the wrong time or are we in the comment phase?

DR. THOMAS: (Off mic).

DR. PROSCHAN: Okay. I'll stop then if we're not --

DR. THOMAS: (Off mic).

DR. PROSCHAN: Okay. Well so -- well I'll wait and say the rest, what I was going to say in the comment phase.

DR. THOMAS: Dr. Lewis?

DR. LEWIS: Thank you. Well I'll actually comment that I'm actually kind of okay with the MACE-plus thing you've got there. But what concerns me is, as near as I could discern from the briefing documents, the physicians in these trials had the ability to manipulate the patient statins and other cholesterol lowering agents at will. And despite that, there is this discrepancy in LDL cholesterol.

And I am concerned about whether there has been sufficient follow-up time of any of the patients in this trial for us to understand the clinical consequences of that, because it's probably going to persist in the real world. Like maybe forever in these patients because you know the doctors could have fixed during the trial and they didn't, even though they were on statins and they could start statins.

And if you could -- and I have a second thing, so I'll say both if it's okay with you. So if you could comment whether you think that this is sufficient follow up to see the consequences, a prolonged increase in LDL cholesterol.

And the other thing is hyperphosphatemia has

been associated with increased cardiovascular mortality, not only in renal patients now, but in the normal population as well, and even within the normal range. And I wondered if you did any analyses of whether hyperphosphatemia was a risk factor for cardiovascular outcomes in this trial, since it's a consequence of your drug as well.

And I will -- just one other electrolyte comment. It does lower uric acid, which you know you don't even list on your maybe good things. However, it is also uricosuric. And I do think whatever happens, that does need to be -- doctors need to be reminded of that. This is a population that eats a lot of purine and could get in trouble with uricosuria here, but should also know that it lowers uric acid.

DR. STEIN: Thank you. With regard to the statin dose changes, the analysis that we've done particularly looked at the statin dose changes through the first six months because we wanted to make sure that that didn't confound the LDL data that we were presenting.

And I think, as the FDA presentation

indicated, there was very little change that occurred. It was slightly greater over time. But I think the comment I'd make is that the mean change is a relatively small one. Not in terms of the discussion around whether that's meaningful or not, and certainly we'll have more of, but in terms of the quantitative change, and given the variability in LDL, I think it may be hard in individual measurement to see these kinds of changes. So we didn't see net changes in statin.

The numbers of patients that were increased or decreased in dose when initiated statin was relatively modest even over the 18 months of the follow up in the broad dataset. And as I said, I think that's just reflects that these were relatively modest changes.

I will say that we asked that the physicians do their best, prior to run into implement statin therapy and then to keep them stable if possible, but they were not proscribed from modifying. And in the CANVAS trial, we asked that they be aggressive about it.

With regard to the time course, as I showed, because of the updated analysis that we were requested to do by the European agency, that was after about 20 months or so, and the hazard ratio wasn't changed. I certainly would wonder whether the one-year time point might be sufficient to see the impact of LDL.

But I think now that we're going further and we're not seeing any further change in the hazard ratio, I think that is likely a sufficient exposure. Certainly in the statin trials we begin to see separations, some trials one, two years, in that timeframe. So I think if we were to see a negative impact, one might expect that might begin to be seen.

With regard to phosphate, no we have not done analysis looking at changes in phosphate relative to outcome, although again, the changes were in the five, eight percent range. They were relatively small. And the only other comment I'd make with regard to the uricosuric comment, we haven't flagged that extensively, but I do want to say that we did look at

renal stones and there was no increase in renal stones. And we have a very large program, we had a fair number of stones, but there was no increase, actually slightly fewer.

DR. THOMAS: Dr. Palevsky?

DR. PALEVSKY: So I'd like to explore a couple things about electrolyte disturbances. You had provided that on the incidence of hyperkalemia, and I think in the FDA presentation it indicated that the potassium went up in patients on RAS blockade or potassium-sparing diuretics, but went down in patients not on those agents.

One would expect, with an osmotic diuresis that there would be potassium wasting and I didn't see any data on the incidence of hypokalemia. I'd also like to know the actual rates of clinically significant hyperkalemia. If a patient goes up from 4.4 to 4.6, I'm not all that concerned about it, but if their potassiums are going up into the upper 5.0s I am. So if you could present data on percent, on the incidence of potassiums greater than 5.5.

I also didn't see any data on changes in

serum sodium concentration. One would expect a risk of hypernatremia with an osmotic diuretic. So if you could provide that information.

DR. STEIN: Sure.

DR. PALEVSKY: Also I did not see, and maybe I missed it, the data on maximal increase in hemoglobin concentration. If you could, provide the data on the peak hemoglobins or peak hematocrits that have occurred because that would be informative regarding the extent of the intravascular volume depletion.

And finally, there was still some question in my mind as to how much of the change in kidney function is purely hemodynamic versus whether there's any development of structural kidney disease. You presented some data in the briefing document on NAG.

Do you have any data on any of the other markers of tubular damage that could have been looked at, Kim-1, which is validated, NGAL, which I don't think the FDA has accepted as a validated marker, or any of the other potential markers of tubular injury?

DR. STEIN: So if I can start with the question about potassium. If we could see 2260,

SA2260. We'll try to pull it out. It's the histogram for the potassium distribution changes. Okay, thank you. So slide up.

This is looking at the distribution of changes in patients who met the outlier criteria. So the outlier criteria was a greater than 15 percent increase, and above the upper limit of normal. The active or placebo- controlled is on the left side, and on the right side with canagliflozin treatment groups.

And I think our conclusion from this is that there is not a notable difference in the distribution of more severe events with canagliflozin in those who met the outlier criteria.

With regard to the patients who had more severe hyperkalemia, it was pretty infrequent and the events that we saw were in patients who had multiple factors. The FDA presentation nicely noted that in patients on ACE or ARBs, the means were slightly increased. What we saw was that the patients who had the more significant values, for example we had one patient who was on aliskerin, an ACE inhibitor, and aldactone, and had CKD, and had a potassium that was

over seven, that was some of the events that we saw.

We saw no changes in sodium concentration --

UNIDENTIFIED SPEAKER: (Off mic).

DR. STEIN: Hypokalemia. If we could pull the outlier criteria for hypokalemia, or for potassium, that will include hypokalemia. But just briefly, no there was no change in occurrence of outliers of hypokalemia.

DR. THOMAS: Actually, before you -- could you go back to the slide. Dr. Proschan, you had a comment?

DR. PROSCHAN: I'm not sure how to interpret that slide. I mean first of all, the scales are different, the Y-axis. And they're number of patients, not percentage.

DR. STEIN: Can you go back to the histogram please? Slide up.

DR. PROSCHAN: So that's number of patients, and they have different total numbers, and then the scales are different. So I don't know what to make of that.

DR. STEIN: I was really just trying to focus

on those patients who had more severe hyperkalemia. So if one looks above six, in terms of the distribution, as you note, there's more patients in the canagliflozin group who met the criteria. But the numbers of subjects with more severe elevations didn't appear to be particularly different.

We can analyze that by proportion. I think we also had an outlier analysis looking at those with more severe values and I think that had percentages. I think that's 2268, if we could pull that up, and that might address that. Do you have 2268 or perhaps I have the number wrong? Slide up.

So here's looking at the levels of potassium. So these are patients who have a potassium that's either greater than 6.5, and so this provides the incidence rather than just the distribution. The second row, greater than 7.0, and the bottom are patients who have occurrences who had more sustained hyperkalemia. And as you can see, the incidents didn't look to us to be notably different from patients with really clinically severe hyperkalemia, 6.5 or 7.0, and the values were not sustained for potassiums above 6.5.

So with regard to structural kidney disease, you asked about biomarkers.

UNIDENTIFIED SPEAKER: (Off mic).

DR. THOMAS: Just can I make a reminder? So one thing is if when you are speaking, remember to have your microphone on. And then if you're not speaking, to turn your microphone off.

DR. STEIN: So we're pulling that up. So we were looking for hypokalemia I think, was the events of hypokalemia.

DR. PALEVSKY: Hyper. If you have hypo too, but hyper is probably --

DR. STEIN: Hyperkalemia? I'm sorry.

DR. PALEVSKY: Natremia.

DR. STEIN: Oh, I apologize.

DR. PALEVSKY: Hypo and hypernatremia.

DR. STEIN: So if you go back to that, we'll --

DR. PALEVSKY: And I wanted hypokalemia as well.

DR. STEIN: Okay, we'll pull that together. So if we could get the -- so this is for sodium. Slide

up please. So this is looking at patients who met the criteria at any time, and for the last value. So the values below the lower limit of normal, with a greater than 5 mL equivalent decrease in the first row and the second row, are patients with events meeting hyperkalemia. And as you can see, there was a very slight increase.

These were consistently very minor, transient increases of patients who had values that were 152 or 149. We saw minimal occurrence of values that were above -- 155 was very uncommon, and these were transient values. And the last (indiscernible) value is the last two rows, but I guess the point I'd make it was that the mean changed very little and very few meaningful outliers.

So for the potassium, slide up, with regard to the both increases and decreases. So the way we looked at it, just to orient you, is we looked at patients who met this criteria at any time during the study, and then for the last value that was still on study drug. And for the potassiums below the lower limit of normal, with a greater than 15 percent

decrease, that's shown there, which I think we thought was not meaningfully different.

For the increases, as you can see, there was no difference between the 100 in the non-canagliflozin group, with a slight increase in the 300 milligram group. But I showed you the distribution. Our interpretation was that these events tended to be fairly modest and not terribly more frequent with the 300 milligram dose.

So with regard to the structural kidney disease, in our Phase II studies we looked at NAG, which is an issue because hyperglycemia and glucose infusion tends to increase NAG, so it's not a particularly good marker with this pharmacologic target. We also looked at beta-2 microglobulin. We did not have Kim-1, but we did look at beta-2 microglobulin.

Slide up. This is from the Phase II dose range finding study. This was a 12-week study in patients with diabetes. The group sizes were relatively limited and we're showing the data here for the two clinical doses, the comparator and placebo.

And our interpretation was there was basically just no notable changes across groups, very small changes.

The biomarker that we took into Phase III was the urinary albumin to creatinine ratio because we thought it was also a useful and validated biomarker, both reflecting protocol glomerular and tubular injury.

And I showed you the data from that, which was consistently across all of the studies in which that was evaluated showing a reduction in patients with baseline albuminuria and no change in patients with baseline normal albuminuria.

DR. PALEVSKY: And I'd asked if you had the hemoglobin data.

DR. STEIN: Yes, we'll see if we can pull that out as well. That may just take a moment to find, so if we can get the distributions and the mean changes, that would be great. That's not the right one, so we'll come back to that. We'll pull that.

DR. THOMAS: Okay, so what we may do is, during the discussion, if you have that let me know.

DR. STEIN: Okay.

DR. THOMAS: At this time, I apologize --

DR. CAPUZZI: Excuse me. I haven't had a chance and my light's been on a long, long time.

DR. THOMAS: So what --

DR. CAPUZZI: And I turn it off to be, you know, gratuitous. But I do want to say something.

DR. THOMAS: Doctor -- be brief, but you know the thing is we haven't been able to get to everyone because we do need to move on to the questions.

DR. CAPUZZI: But there's an important issue.

DR. THOMAS: Go ahead, but be brief.

DR. CAPUZZI: Okay. Now I just wanted to ask you, the -- there was this one line within the materials that were sent about an NMR LipoProfile change, which looked possibly problematic, and nothing else.

Now, did I understand at the end of the last session, that in the CANVAS trial it was shown that the plasma lipoprotein profiles were better, or that there were no untoward effects on these particles that would make them more, in any way, a problem for the development of the drug? I mean I'm not looking for a problem.

DR. STEIN: I can show you the results from that.

DR. CAPUZZI: No, I'm just -- please. There is not time for that. Were there any untoward effects from the -- or improved effects that really show that there are not an issue with the lipoproteins? We have to move quickly.

DR. STEIN: Well the particle changes that we saw was a relatively small increase in particle number.

DR. CAPUZZI: Right.

DR. STEIN: The increase was -- we saw a larger proportionate increase in the large particles, and a small proportionate increase in the small particles. There was no change in small particles at the 100 milligram, and about a three, five percent increase at the 300 milligrams. Does that answer your question?

DR. CAPUZZI: All right. That answers one part. But the other point I'm making is, were there any changes in plasma lipoprotein levels? That was one thing I wanted to know.

DR. STEIN: We did measure Apo protein B.

DR. CAPUZZI: Right.

DR. STEIN: And the increase in Apo protein B was about half the extent of the increase in LDL cholesterol.

DR. CAPUZZI: Well they're both parts of the same animal, so that's not good. Is there anything favorable about the changes in lipoproteins?

DR. STEIN: We haven't measured other Apo lipoproteins. I mentioned that there's an increase in HDL, a decrease in triglycerides.

DR. CAPUZZI: All right. HDL cholesterol, right?

DR. STEIN: And total cholesterol change is very, very little.

DR. CAPUZZI: But not the part -- but the A1 protein, the business end of it, just the HDL cholesterol?

DR. STEIN: No, we don't have A1 levels.

DR. CAPUZZI: Okay. You know I just wanted to make a remark. This is a very important issue with this drug and I'm just going to make a suggestion, and I really don't mean to sound in any way disrespectful.

But the CDC, 16 years ago, put out a green book, the laboratory measurements of lipids and lipoproteins for study, and for getting correct results. It doesn't say all that, but that's what it is, it's a green --

And it goes into great detail, not only about how you measure these, but how the patient is prepared, both in terms of their diet, the lack of other illnesses, not lying down. It's a very important thing to get correct data. I'm not trying to be obnoxious, right, so please. This should be done correctly.

And it's not just the measurements and the way you're measuring, it's how the patient's prepared, you know psychological or trauma or things like that. So I just wanted to make that suggestion for the rest of your studies. And I stop. Thank you.

DR. STEIN: Thank you. Questions to the Committee/Committee Discussion

DR. THOMAS: So we'll now begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate, except at the specific request of the panel.

And we'll start with question one. Based on the information provided in the briefing materials and presentations at today's meeting, please weigh the benefit risk profile of canagliflozin in the population of patients with type 2 diabetes and moderate renal impairment.

In your discussion, consider and comment on the following: the impact of renal function on the glucose- lowering effect of the canagliflozin; the impact of canagliflozin on the risk of renal function deterioration; the clinical importance of observed volume and electrolyte related changes associated with canagliflozin use to the overall safety of this population; the clinical importance of the observed increased risk of genitourinary tract infection associated with canagliflozin use to the overall safety of this population.

So just let us know if you have some comments on question one. Dr. Lewis?

DR. LEWIS: So I'll begin the discussion I guess. So there's things about its use in the population of patients with decreased renal function

that I find disconcerting. Despite an increased area under the curve at the high dose, which I'm not sure I was totally -- my concerns about that in renal failure patients were totally assuaged by the fact that for 12 weeks somebody got CANA 300 BID and pharmacokinetically it looked that would be okay if you had renal failure and got those kind of areas under the curve.

Despite that, there's less glucose lowering effects in them, so it's less efficacious, and yet there are as many or more side effects in them. So I think that we almost have to look at the risk benefit of it in them as a separate population, which a little bit impacts on how the next question I think is worded. Because I think it is quite different in them than it is in the general population. I hate for my patients not to be able to get a drug, so, and I hate it to be limited, but I'm concerned about it doing more harm than good in them.

The impact of it on renal function deterioration, I feel better looking at the histogram, that there isn't sort of a hidden -- like those mean decreases in GFR aren't reflecting a subpopulation that

are just having horrible things happen to them.

It's still almost hard to believe that it won't cause more acute renal failure associated with other illnesses, because they're relatively volume depleted. However, I would say that it is not the same as giving a diuretic to have an osmotic diuresis, but we put these people on diuretics all the time and they probably have some relative volume depletion. So I'm somewhat -- I'm less worried about that.

The only electrolyte issue I am a little worried about is I don't know that we thought enough about the impact of the hyperphosphatemia. I didn't hear anything about FGF-23 data or anything like that, which you would expect to go up with hyperphosphatemia, or with higher phosphorus' I should say, not necessarily hyperphosphatemia.

And the only other last comment I have on your last bullet point is obviously urinary tract infections are important in this population, as are any kind of fungal infection and all kinds of hygiene issues. In addition, I think it means that one of the most commonly used drugs, with this drug, may turn out

to be Diflucan, which is a cytochrome P450 drug, which this drug, at high doses, has potential to maybe do something with, which we didn't get addressed but I think should be addressed.

It is not one of the drugs that they specifically said wasn't going to interact with this drug. And I think that's an important thing to know that it won't, for the physicians who are going to use it. So I'll pause there for further discussion.

DR. THOMAS: Dr. Palevsky?

DR. PALEVSKY: So I'm going to basically agree with Dr. Lewis's comments. I'm not surprised that we see a lesser glucose lowering effect in patients who have underlying decreased kidney function. Since the mechanism is loss of glucose in the urine, and with a decreased GFR, the degree of glucose -- the magnitude of the glucose loss will be decreased because the filtered load will be proportionately lower.

I'm also concerned then that with a decreased benefit, that the risk profile may be altered. And I'm not sure that we have enough information -- this is already a population then that is at increased risk for

cardiovascular and other complications, and I'm not sure that we have sufficient information in that population. And I think that we're going to need, if it is a drug that then gets approved, that we're going to need post- marketing information, focused on that population.

I have relatively -- I'm relatively comfortable with the decline in kidney function that's seen. I do suspect that it is predominately hemodynamically mediated. One interesting question that I've not heard any, and don't know any information on, and couldn't find, is there are patients who have congenital glucosuria, presumably due to mutations in this transporter. And I don't know what the long-term history in terms of development of kidney disease is in them. My understanding is that it is an entirely benign finding, but any additional information from that natural occurrence of this would be I think helpful in considerations as to what the risk on kidney function is.

The electrolyte and volume depletion issues are not particularly disturbing to me, although there

may be a need for caution of use of other diuretics when this agent is being used to prevent clinically relevant hypovolemia. And in fact many of these patients have problems with volume overload underlying so that it may be beneficial from that standpoint. And I have no other comments beyond what Dr. Lewis said in terms of the GU infection.

DR. THOMAS: Sponsor, did you have a comment, a brief comment?

DR. STEIN: I was just going to briefly comment that -- two quick things. One is, in terms of SLGT2, deficiency states, the genetic deficiency, it's a wide range of urinary glucose excretion but some individuals with urinary glucose excretion in this range. And it's not a very well-characterized disease because it's infrequent, but there aren't reports of any untoward long-term effects. Occasional patients report in the literature with long-term follow-up without any report of a phenotype that implies a renal structural injury.

I was also going to just offer that I do have some additional renal safety information in the CKD

patients, and be more than happy to show some of the outlier analysis and longer term follow-up if that would be helpful.

DR. THOMAS: Would that be helpful to you, Dr. Palevsky?

DR. PALEVSKY: Yes.

DR. THOMAS: Okay. Go ahead. While you're getting that slide up, Dr. Kaul, you had a question, or comment?

DR. KAUL: Did I hear them say that in the familial glycosuria there are no major problems? But we have numerous examples of genetically-mediated diseases, lipid disorders, where we don't have a higher risk of coronary artery disease as a glyceride disorder. And so I don't find that reassuring.

DR. STEIN: So let me just very quickly show two pieces of information. You were asking about longer term effects. Slide up. We do have data from the 3004. This is the dedicated study in subjects with a Stage 3 CKD, baseline is 30 to 50.

And what we saw at week 26, which I earlier showed, we see the same course, which is that there is

a continued attenuation with a rise in the eGFR back towards, not to baseline, in the 300 milligram group but to baseline or to the placebo group level with 100 milligram group.

We've also looked at the outlier analysis. Slide up. I think you saw some data during the FDA's presentation regarding the any time value, so I thought it would also be useful to present the last values. Because we expected to see, with the any time values, the greater than 30 percent, because there's a reduction in eGFR, a shift to the distribution to the right, you get a lot more patients who are hitting the criteria.

But when you look at the last value, so this is the last on-study drug value, and this is in the 1,000 patient pooled renal impairment dataset on the top, you can see that the numbers meeting the criteria of greater than 30 percent is not meaningfully different across the groups. The dedicated study is shown on the bottom, this is the DIA3004 study, where again I think supporting the same conclusions.

And I think you were also asking about

events. And I would just comment that the MACE-plus events were not increased in individuals with CKD. In fact, if anything, the trend was in the opposite direction.

DR. THOMAS: Any additional comments? Dr. Kaul?

DR. KAUL: I think I heard this morning somebody say that the prevalence of moderate renal impairment in diabetic population is somewhere around 20 percent. And if that is the case, then the moderate renal impaired population in this dataset was underrepresented at only 10 percent of the total dataset.

And I have questions in my mind whether the 40 to 50 percent attenuation of the glycemic efficacy in this population is clinically meaningful. You know if you have a quarter of patients achieving goal hemoglobin A1 less than seven, or (indiscernible) patients at the higher dose, is that clinically meaningful?

But I also heard in the presentation this morning that we're striving for a target of over 50

percent. So I'm not quite sure whether the benefit risk balance in this underrepresented, moderately impaired renal function dataset is in favor of benefit.

DR. THOMAS: Yes, just --

DR. STEIN: I was going to offer that one of our experts that we have with us has expertise in the management of renal disease patients with diabetes. And if it would be useful, I could ask him to comment on the issue around clinical value because I think the context of limitations of the options in these patients has to be considered relative to the options in patients with more normal renal function. So if that would be useful, I could ask Dr. Bakris to come up and perhaps comment on that just briefly.

DR. THOMAS: Would that be useful to you, Dr. Kaul? Okay, as long as it's brief. Thank you.

DR. STEIN: Dr. Bakris?

GEORGE BAKRIS: Very quickly, I want to just agree with the comments that Julie and Paul made because they're right on the money. I do want to say that there's a review that is coming out in about two months in Nature Nephrology, that we just finished, on

looking at non-insulin glucose-lowering agents in people with advanced kidney disease and on dialysis.

There's a grand total of five agents, and most of them in reduced doses, half of whom either cause edema or hypoglycemia. So there really is a very small proportion of people -- a small proportion of drugs that is useful in these people. If you, because I do agree to a certain extent in terms of if you take the group below 45, I think Julia's on the money, the risk may outweigh the benefit there.

But if you take the group 45 to 60, you're getting 0.5 percent reduction, you add that to a little low-dose PIO and a little low dose of something else, and you may be in target if the patient's adherent with their diet. So I don't think you should throw the baby out with the bathwater. I think that's a very important point.

And, you know, it is about 30 to 35 percent of people that actually have advanced kidney disease, not on dialysis, but that is the number one cause. And this is a growing population in many ways, girth as well as other things. And I think that we need to

offer to some options, as you heard actually from the public commentary. Thank you.

DR. THOMAS: Thank you. Any additional comments for question one? Dr. Palevsky?

DR. PALEVSKY: I just want to point out that in the elderly, the eGFR is decreased in large part because the formula includes age as a major component. So that if there wasn't availability of the drug based on eGFR of less than 60, it would exclude the drug from a large portion of the elderly population, who have aged into CKD Stage 3 with really near normal kidney function.

DR. THOMAS: And also one other thing I thought maybe one of our cardiologists or nephrologists might want to discuss this. Though I didn't see any -- there is no data, any comments on the dosing in terms of what dose you might want to start out with because of the adverse side effects. Dr. Lewis?

DR. LEWIS: So the sponsor suggests that they start, if they have renal insufficiency, with the 100 milligram dose. Since the 100 milligram dose is totally non-efficacious practically, everybody's going

to get put on 300. And I don't think we have any information about why it would be safer to start at 300 and then go to 300. I mean I didn't see any studies designed that showed that was safer or better. So you know I still am concerned about the risk benefit in people in the low GFR group. And I'm willing to say low GFR is less than 45 I mean, but the low GFR group.

DR. THOMAS: Any additional comments? If not I'll summarize the discussion so far. The drug seems to be less efficacious in glucose lowering as renal function decreases. We have no apparent reduction in side effects, so there potentially is an adverse risk benefit profile in people whose eGFRs are lower. And as a result, is the glucose lowering meaningful in this population?

And it depends how you break this down. If you were to look at the population in the study, which is an eGFR of 30 to 60, maybe the cut-off point is less than 45 or it's not as useful to have the medication or drug versus those who have a between 45 and 60.

The lowering that you see of the eGFR doesn't seem to be as worrisome after looking at the histogram.

There doesn't seem to be a defined subgroup that's at risk. And it's presumed that the lowering is based on hemodynamic changes. And I think one needs to see is that stable over time, and at least from the data shown, that seems to be relatively stable, or would it progress if people are using this for an extended period of time.

It's surprising that there are not more events of acute kidney injury due to the dehydration and volume depletion that's seen early on, which is a little surprising because of the way the drug is seemed to be work (ph). There is some concern about the increase in phosphorus, not for the sake of hyperphosphatemia, but because of the link to other diseases like cardiovascular disease. There weren't any measurements shown of agents that modulate phosphorus, like FGF-23, but that might be useful in follow-up studies.

There's also a concern about the effect of this drug in a population in terms of CVD, that's already risk for CVD. So it the drug is approved for use, in addition to cardiovascular trials that are

being done for the general population at risk, there may need to be more focused studies in this higher risk renal population.

There's a strong concern about the imbalance of genital urinary infections. Not only is there an increased amount of early infections, there's a high rate of recurrence. And one of the concerns as for the fungal infections, there'd be increased use of agents like fluconazole.

And fluconazole has P450 enzyme effects, and this would have interactions with potentially other medications that patients may be taking at the same time. So that will be a concern in terms of drug-drug interactions, not necessarily with this agent, but with other agents that patients are taking.

Finally, if you look at -- well not finally, but if you look at, there are individuals who have SGLT2 mutations. And though this is rare, there's no apparent understanding of any long-term complications. However this should not be reassuring.

As Dr. Kaul brought up, there are numerous examples of genetic disorders that seem to have no

apparent side effect, yet have pathogenic or pathophysiologic effects in patients without that mutation. And one classic example is hypertriglyceridemia. Isolated hypertriglyceridemia doesn't seem to have cardiovascular risk, however we know triglyceride elevations is a cardiovascular risk factor.

If you look at the labeling in terms of if it's just eGFR, the elderly, by the nature of the formula and calculation, many elderly will have a low eGFR without actually having compromised renal function. So there should be some consideration about what's the best way to allow elderly patients who might be appropriate for this drug to take this beyond the eGFR measurements.

And it's not clear if at the dose of at 100, you're really going to get any benefit, so what's the best way to start this drug. It was suggested by the sponsor, in the impaired renal population you start at 100 and then potentially go to 300. But because of the efficacy, it's almost clear that everyone's going to be at 300, so there needs to be some further refinement of

the process of initiation of the drug and dose in the impaired renal population.

Is there any additional comments or corrections to what I said? Dr. Cook?

DR. COOK: Let me just add one other point about that starting dose of 100, in that in this population we also see that they have the greater problems with intravascular volume depletion at the 300 dose. So if most patients are going to be up titrated quickly to the 300 dose, then that is the higher risk population for the intravascular volume depletion, which would be a concern.

DR. THOMAS: So add to that, to the comments about the intravascular depletion at the 100 versus 300 dose. And Dr. Lewis?

DR. LEWIS: Can I make a clarifying comment to what you said?

DR. THOMAS: Sure.

DR. LEWIS: So eGFR just takes the serum creatinine and informs it with age, race and gender. So delta eGFR is delta creatinine in -- because people's race and gender generally don't change, they

don't age that much. Older people have lower muscle masses for any given creatinine. They actually do have a lower GFR and people do -- there's at least a body of literature to suggest many elderly people do lose renal function with age.

I think the comment that -- the point he was trying to make is not that older people wouldn't have a lower eGFR, but that it would eliminate a lot of older people if you eliminated them based on eGFR. However, a healthy elderly person is not going to have a GFR less than 60. So if you used the less than 45 cut off, I think the elderly who had relatively normal kidneys and had just aged would be okay.

DR. THOMAS: And that's what I intended but you said it much more eloquently so we'll go with your comments. Okay. We'll move on to question two.

In analysis of clinical fractures across the Phase III development program, a numerical imbalance not favoring canagliflozin was seen in the incidence and in the exposure-adjusted incidence of fractures. The disparity appears to be driven by low-trauma upper limb fractures and to a lesser degree by spine

fractures, with little differences in lower limb, pelvis or rib fractures.

Comment on the clinical significance of this finding on your overall assessment of safety. In your discussion consider the following: the relevance of observed changes in calcium, phosphorus, parathyroid hormone and 1,25 dihydroxy vitamin D levels; the relevance of changes to bone turnover markers; the relevance of the bone mineral density changes at 52 weeks in the dedicated study in elderly individuals, DIA3010; the clinical importance of the bone and calcium metabolism-related effect associated with canagliflozin; the use to the overall safety of this population and in the renally-impaired population.

So if we have any comments or thoughts from the panel. So while people are thinking, I can get started. It's fairly well-known that with weight loss, whether by diet or other medications, or to gastric bypass, that you will see alterations in calcium metabolism. And you would also see effects on bone density.

Some of that is presumed to be the decrease

in weight. Actually the decrease is -- actually the bone density is less stress on the bone. And if you look studies that look at bone density after gastric bypass, you see a reduction in bone density.

So I think the question I have is, is this a limited effect. We presume that the weight loss plateaus, and if that's the case, then the potential bone density reduction should plateau as well. If the weight loss doesn't plateau, or there's an independent effect of the agent on bone density, then we can consider that would get worse.

So I think one year necessarily is not sufficient for follow up. And I think for a long-term study, whether this is pre- or post-marketing approval, probably we do need some type of long-term on fracture study. I think it's quite concerning that you're having potential risk but it's not clear that there is of fractures that are fragility fractures.

Now this is a population you would think that may get fragility fractures, but men at that age don't necessarily get them, though there is data that type 2 diabetes, the population does have some increased

osteoporosis. So that would definitely need some type of follow up.

So the first one would be bone density, in terms of long-term follow up, and also long-term changes in calcium and vitamin D and parathyroid hormone. I don't think actually the magnitude of the changes is worrisome; it could be just related to the weight loss.

The bone turnover markers also seem to go on the line. You would see increased reabsorption markers. The one thing that's also related, which I didn't think we got into, is this population is also probably postmenopausal, but there could be some perimenopausal people and that might have some impact, though generally there was menstrualized (ph) women especially in the cardiovascular trial overall. But the bone density studies was in an elderly population so you presume they're postmenopausal.

The last thing is, related to this is, you know this is an agent that, unlike many other diabetes agents, we tend to think of a progression. We use an agent, then we stop it. We add another agent.

We go on to insulin. There are very few agents that we tend to keep, that are all medications for the entire course of someone's diabetes care. Metformin probably is one of the exceptions.

This agent is an agent potentially you could use throughout someone's diabetes care because of the mechanism of action. And the fact that there are individuals who are younger, who have type 2 diabetes, and though I don't think it's going to -- essentially in the label, there is always the potential, if one of our former panel members were here he probably would have brought it up, that it could be used in a non-type 2 diabetes population.

And the concern I would have if alterations in bone density, is if you have young enough individuals, teenagers, 20-year-olds, they're developing peak bone mass, where does that leave them down the road? For short-term fracture risk, they're not going to have that.

But if they're on this agent for 5, 10, 15 years while they're developing peak bone mass, and after the accretion of peak bone mass, will that lead

to earlier osteoporosis and fractures in their 40s and 50s versus 60s and 70s?

So I think there's a lot of long-term follow up that has to be done. And not necessarily all that can be in a trial, so it probably should be registry based. Any other comments? Please.

DR. STEIN: I was going to offer two points. One is that we have done some analysis to look at the association with weight loss. I'll also say that we've consulted extensively with Dr. Bilezikian, who is here with us today, including on the question of the likelihood of progression of the bone overall density changes from the analysis we've done at week 52. And if the committee would find it helpful, I'd be more than happy to ask him to comment on that.

DR. THOMAS: Dr. Bilezikian, if you want to comment briefly on that, that would be fine. And specifically on the topic if the bone related changes would persist beyond the one-year follow up.

JOHN BILEZIKIAN: Bone would be the forgotten subject today. I'm John Bilezikian and I'm head of the Division of Endocrinology and head of the Metabolic

Bone Diseases program at Columbia. So the question of the long-term follow up is obviously relevant. But there's some short-term effects that we've all noted, and it certainly cannot be explained by changes in bone density.

Whether you use DEXA, the changes are so minimal as to be well within the precision of most of our instruments, but even if you look at the QCT data, where the changes are a little bit greater and we typically see more by QCT. But whether or not that's of concern, I honestly don't know.

But the finite element analysis of those high resolution images do not show any changes in bone strength. So taking that and the essentially less than dramatic changes in hormonal numbers, yes bone turnover markers go up and that may well be related to the weight loss, as the small change in bone density.

So we're left with an early imbalance in upper limb fractures, and that is perplexing. Those are very unusual places to be predominately fragility fractures. And the early course is also quite atypical, particularly if you're going to focus on bone turnover

markers and bone density, where you almost always see those changes first, and then you see the fracture events.

So there's really a mismatch here with regard to trying to put this all together. And I therefore think that the early imbalance is probably not related to bone density, to bone turnover markers, to metabolic parameters, or to bone strength. There must be something else. If there is something else, there may not be because it's an imbalance, it isn't a statistically significant change.

UNIDENTIFIED SPEAKER: If you could also comment on the likely time course past week 52.

JOHN BILEZIKIAN: Yes. So I would -- yes, we don't know of course. But my postulate would be after week 52, when weight loss is no longer an issue, that these curves will smooth out. That would be my prediction. And of course we will find that information out in time.

DR. THOMAS: Thank you. Actually, based on that, there are a couple other things I would also suggest, that may be of useful consideration. One is

we've seen, years after the approval of the TZDs, the increased fracture risk, and it wasn't your typical fractures as well. And once that was highlighted, there were additional mechanistic studies that were done looking at bone biology.

It wouldn't be unreasonable to suggest that some of those studies be done now, looking at bone progenitors. And it may not be unreasonable in a subpopulation to look at bone biopsies to see if -- I think once the weight loss phase is gone, and also to look at the early phase to see there's some changes that might be helpful in elucidating what's going on. Dr. Lewis?

DR. LEWIS: So I guess the last three words are in the renally impaired. And I would just say this is another example where the hyperphosphotemia and decreased 1,25 vitamin D are the big initial features of renal osteodystrophy in renal failure patients. Anyhow we consider that to be a really bad consequence of renal failure. And not only associated with bone disease, it's debilitating but cardiovascular disease, valvular heart disease, all kinds of things we think

are bad.

So this is another sort of example where, in this subpopulation, they're going to pay potentially a bigger price for this side effect of the medication, because it does two bad things that are bad for them anyhow.

DR. THOMAS: Any additional comments? Since I did most of the talking, I can't write and speak at the same time too, also. If you could just use my comments to summarize, plus Dr. Lewis's, that would be fine. Well people can disagree with me, that's fine. But okay, so we'll move on to question number three.

The cardiovascular risk associated with canagliflozin use was assessed in a prespecified meta-analysis of adjudicated cardiovascular events across nine Phase II and III clinical trials using a composite endpoint, MACE-plus, that combines cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina.

Based on the information provided in the briefing materials and the presentations at today's meeting, please discuss the following: whether results

based on the pre-specified Cox proportional hazards model are reliable; your level of concern regarding the apparent imbalance not favoring canagliflozin in early, less than 30 days, MACE-plus events observed in the dedicated cardiovascular outcomes trial, DIA3008; the divergence of risk estimates for the components of MACE- plus in the prespecified meta-analysis in which the hazard ratio for nonfatal stroke exceeds 1.0, while the other components are below 1.0; the clinical relevance of the observed changes to blood pressure, weight and low density cholesterol levels toward informing overall cardiovascular benefit risk associated with canagliflozin use. Dr. Brittain?

DR. BRITTAIN: Well I'm pretty comfortable with the overall hazard ratio estimate. Even if there is some non-proportionality in the hazards, I don't think it's very great. And even if it is, it's still going to be a pretty good measure of the overall treatment effect. So I'm not that concerned, particularly since a number of sensitivity analyses were considered. For example, in the non-CANVAS studies, the results look quite good.

And in the CANVAS studies, even though we do have that concerning first 30-day period, once that -- you know, the survival curves turn around. And not only cut -- you know converge, they seem to -- there's some suggestion that there may even be a possible advantage at six weeks, just a suggestion, I mean six months, just a suggestion of that. But when you put all that together, I'm pretty comfortable that the hazard ratio estimate is a fairly reasonable measure of the treatment difference.

I'm not really sure what to make of the first 30 days. Again, because the survival curves do turn around, so I'm not -- you know, even if that were true, that there was some excess at the very beginning, if the survival curves do turn around, I'm not sure what the importance of that is. And so I don't know.

And with respect to the stroke, I guess the fact that the -- to me, at least it's comforting that the non- fatal MI and the fatal cardiovascular events are going the other direction makes the fact that the stroke exceeds one, with a confidence interval around it, less of a concern. And I think, you know, if it

had been the cardiovascular death that was exceeding one, I would be more worried.

DR. THOMAS: Dr. Hiatt?

DR. HIATT: So I'm a little more uncomfortable with whether there's a proportionality throughout, on the MACE events. I mean the first point is that the totality of the evidence should drive the thinking and the confidence intervals around the data so far are below 1.3 of the upper bound.

So that's, you know, it's clearly below the guidance threshold. So one could easily stop there and conclude that there really is no cardiovascular signal at all. But I do think that the divergence of events, early versus late, at least raises a signal of concern but it's certainly not definitive.

And so then the question would be is that just a numeric imbalance that occurred by chance, or is there some mechanism that could maybe drive that? And so I was struck by the clustering of hypotensive events, hypovolemic events that occurred early.

I recognize the sponsor and the FDA went to lengths to demonstrate that there was no clear

relationship. But I'm not sure you could easily find one. You know, I'm not sure that the hypotensive event was necessarily at the same time as the CV event. But certainly the fact that these two things were occurring does raise concern.

So then you ask well, the sponsor's also made a point that lowering blood pressure with this agent is a good thing. And so I think back actually eight years ago to a cardio renal meeting where we reviewed anti-hypertensive agents and came to the conclusion that blood pressure drugs that lower blood pressure by and large prevent CV events.

And it turns out that different agents, using different mechanisms, get there through different mechanisms and maybe change components of the composite slightly differently, but overall there's a benefit. But we didn't really take on the issue of lowering blood pressure by osmotic diuresis, which I think is kind of a non-physiologic way to lower blood pressure.

And therefore, if you look at that mechanism compared with the adverse event profile and the time to first event being quite striking in the first 30 days,

and then look at least a numeric imbalance in the early first 30 days, it just raises concern to me that I think we can't ignore.

So are there other examples of treatments that do that? And there are. I mean there are things like bariatric surgery that early on you have excess death, in the perioperative period, but then as the treatment, surgical treatment takes hold, then those curves reverse quite clearly. And that's true for some other procedures like carotid endarterectomy where you know you take a hit early because the procedure you know has a perioperative risk. But once that risk is resolved, then the benefit accrues over time.

So the question here is are patients really taking a hit or not? I mean I can see where a patient with cardiovascular risk, particularly in the CV outcomes trial, would have a higher risk of hypovolemia and hypotension than a healthy younger person. And so the fact that pooling of the data from those other trials didn't show that doesn't surprise me.

The other piece of this puzzle I think is the late risk. And you know the lipid changes I think are

fairly, I'm not going to call them striking, but I think that there's no doubt in my mind that if you look at the LDL, the Apo B changes, that there's really an adverse effect on lipids here. And so this non-proportional hazards curve looks like it's kind of coming back down again at the end, and of course that's because there's not many events out there and the certainty goes away.

But you know it does sort of make one wonder if we're not sort of looking a little early here and wondering what the cumulative total risk assessment might look like when the CV outcomes trial's actually completed.

So that I think there's two components of this risk equation that make me concerned. The early hypovolemic, hypotension risk, paired with this sort of imbalance, and then the late risk which has not been fully evaluated because, in terms of changing lipids, you know if we lower them with statins, the curves don't separate right away. And so if we raise them by some other mechanism, I don't know how long it's going to take to see that consequence. So I think the

dataset's a little incomplete.

And I think these markers that we're seeing here at least make one pause for concern. But you know, the totality of the evidence, the point estimate, the confidence interval, obviously that's very reassuring. But I'm not completely satisfied that that's the complete story today.

DR. THOMAS: Dr. Proschan?

DR. PROSCHAN: I'd like to actually suggest a correction on bullet number three. It talks about the hazard ratio for non-fatal stroke exceeding one. It was my impression that that was, that 1.46 compared was all stroke. If it's just non-fatal stroke, then I say that analysis doesn't make sense because then you'd have to sensor fatal stroke, which would be ridiculous.

So I think that corresponds to all stroke, right? Fatal and non-fatal. The sponsor had F and -- you know, made it look like it was fatal and non-fatal.

DR. THOMAS: Dr. Guettier?

DR. GUETTIER: That's correct, it's actually all strokes.

DR. PROSCHAN: All strokes, okay good. Okay,

so with respect to the business about the first 30 days, I think this is a really tough thing to try and figure out. Because even if you had specified in advance, I think there might be a difference in the first 30 days versus beyond that, then the P-value is still not significant, or at least you know it's questionable.

But the fact that you didn't do that, the fact that you looked at the curves and looked for places where it might seem to go the wrong way for a while and then look better, it makes it much more difficult to interpret any kind of P-value.

So for example, when you look at the curve and you say okay, look at these first 14; 13 of them were in the drug group. You know, you're sort of picking the worst spot.

So it's very analogous to monitoring a clinical trial after every new endpoint, computing your P-value after every new event, and then looking, is there any place for which that is going the wrong direction a significant amount?

And if you have a large enough trial, there's

actually a pretty high probability of finding at least one spot where it seems to be going the wrong direction. Yet even though you know you're looking for this place where it goes the wrong direction, it still doesn't come out significant by conventional means.

So that tells me that you know the evidence is by no means convincing that it's going the wrong way, that that going the wrong way is real. However, of course, you know I can't say it's not true, it's just that the evidence to me is not really that compelling, especially when you consider you know the 2:1 randomization that would make 13:1 otherwise sound really striking.

But even if you grant that, even if you grant that there is a real difference, early versus late, I still think it's reasonable to sort of combine those, look at the overall hazard ratio, and conclude that things are pretty good.

As far as the stroke, you know that is disturbing and I don't know whether that's real or not. But I think if it were real, I think you would tend to see the same thing with some of these other

cardiovascular outcomes. So I'm largely satisfied with the cardiovascular events, not completely of course, but largely satisfied that they've shown what they need to.

DR. THOMAS: Dr. Knowler?

DR. KNOWLER: Well I'll be brief because what I wanted to say has been said, but I did want to comment on the proportionality since I had raised questions about that. I basically completely agree with what Dr. Brittain said, and I won't repeat that argument. It's not a concern for me.

From the data we've seen, I see no concern about cardiovascular disease. But with the lipid risk factors, I certainly am concerned that in the long run something might develop, and so I think the story's not finished yet.

DR. THOMAS: Dr. Kaul?

DR. KAUL: Yeah, with regards to the first issue, I agree with the expert statisticians. I don't think that's a major issue. I have some degree of discomfort in trying to figure out what to make of this cardiovascular outcome data. I mean the fact that we

don't see this early hazard in the non-CANVAS dataset can easily be explained on the basis of what Dr. Hiatt just mentioned, that the CANVAS trial population is a higher risk population. It's particularly prone to some of these hemodynamic events that were not captured because the first visit was at six weeks and it might have -- they may easily have missed that.

In terms of the hazard ratio, they appear to meet the criteria, but I was more interested in looking at what the clinical impact of those data are in terms of the totality of data. I would have liked to have more information about what was the clinical impact of these stroke event rates. What if most of these strokes are disabling, and what if most of the MI benefit is driven by biomarker criteria of MI, of questionable clinical relevance? And I was not able to make that balance in my head.

Yes, there is 16 out of the 37 cardiovascular events were contributed by fatal MI and fatal stroke, which is less than 50 percent. So where are the other cardiovascular evidence coming from? So I had some difficulty in sort of formulating.

There is uncertainty. The follow up, I would like it to be longer, two-year follow up to see what would be the impact of the lipid profile. Is this LDL elevation something of potential concern or not?

And then I have concerns about the trial design. If I heard the sponsor say it correctly, CANVAS has two sets of endpoints. There is a primary composite endpoint for the prespecified combined or pooled MACE meta- analysis, which is the MACE-plus endpoint. And then the original endpoint was a stringent MACE endpoint. And how do you control for the type one error?

I mean in the briefing document, on Table 39, we see the alpha errors presented, but that's presumably for the MACE-plus meta-analysis endpoint. How do you control for the original primary endpoint, which was the MACE? So I have issues with that.

The other issue I have is that, and I think the FDA will have to really think long and hard about this, how do you allow an interim analysis to impact on your regulatory decision-making? And the reason why I say that is because let's say the drug gets approved.

How do you ensure that the trial integrity is preserved? How do you make sure that the crossover is minimized? What if after the drug gets approved, the patients who are randomized to the control arm want to be on the active treatment? That will sort of shrink the differences and bias the upper bounds towards the null, and make the drug look safe from a cardiovascular point of view.

I think -- I'm sure the FDA is already deliberating this issues and I acknowledge that the guidance document is a work in progress and that it's through these interactions or deliberations that we will make more progress in terms of what advice to offer to the sponsors. So those are some of the concerns that I have in regards to the cardiovascular dataset.

DR. THOMAS: Dr. Savage?

DR. SAVAGE: I'll try to be brief because I'm really repeating some of the things that have already been said. But I basically agree with what Dr. Hiatt said, I have concerns about the fact that although the overall cardiovascular data look reassuring, you're

making an educated guess if you actually draw final conclusions based upon that.

I think that clearly some long-term follow up is necessary to particularly find out whether there's any adverse effect of the lipid changes that have been documented. And I might mention that about 15, 18 years ago, when rosiglitazone was first coming out, notice was taken of the fact that LDL cholesterol was elevated in patients on that drug, and the claim was made that the particle sizes and so forth were such there wasn't anything to worry about.

So I agree with some of the comments that have been made, that in this particular case it looks like the risks are not as -- you know there are some reassuring data here also. But there's no doubt that there needs to be a long-term follow up.

And the issue that Dr. Kaul raised as to these designs and whether this particular design of the way the trials are being done may raise some design issues. I think I'd leave that up to the people with more expertise in study design to deal with.

But I would like to point out that in a way,

the fact that there is an ongoing trial right now means that we'll have better answers to some of these questions within a few years.

If we were in this situation today, and the other trial had stopped and someone had just -- and the company had to mount a whole new trial and go on for several more years to get five-year data, it would be eight or 10 years before we'd have the data. And this way we'll get the data more quickly.

So, you know, I think the FDA people have to weigh all the pros and cons of the design issues, but this is an example of where the attempts to figure out how we could design something that wouldn't block the development of diabetes drugs, because of extremely high cost to get them initially approved, could pay off, that we've got something in place.

DR. THOMAS: Dr. Brittain, you had a comment on that?

DR. BRITTAIN: Yeah, I just wanted to make sure -- I want to get the FDA perspective on. You know, the CANVAS trial's ongoing. And they said they were going to wait until they have 500 -- go until they

have 500 events. What would be, if the drug's approved in the short term, what is the process then as that data accumulates? If, in fact, the long-term data do not look good.

DR. PARKS: So I'll start off and then see if Dr. Rosebraugh or others members of the team want to weigh in. Currently how it stands with the cardiovascular, the CV guidance for diabetes drugs, is that they need to first provide us the reassurance of a higher threshold of risk. Again, I've mentioned earlier that this sets up a reasonable bar for these companies.

It should be, going to question four, is that if we -- if you think that there is really no concern here about them having been able to successfully discharge that, or rule out, exclude that risk, then the expectation is that, after approval, they still have to demonstrate that there's an unacceptable risk at a lower risk margin, the 1.3. And that can be done in several ways.

Now you probably noticed we did not ask you the question on whether -- what source can be, form the

basis for them to exclude a more conservative risk margin? I think that everything that has been raised at the table here today regarding the interim analysis, the cholesterol, the increase in the LDL cholesterol, the partial unblinding of this trial, these things have been considered by the agency internally as well.

So that is something that we have to consider as to what is the level of evidence that they must provide us to be able to reassure us of not having at least a 30 percent excess in cardiovascular risk.

DR. THOMAS: Dr. Capuzzi?

DR. CAPUZZI: Yes. I just have one minor point to make. Aside from insulin, this is the only medication class that has an action without involving insulin. I don't know if anybody else can think of one, but this is the only one I could think of one.

And it actually might have more utility in a patient that needs therapy but has more preserved renal function. Because the kidney, as everybody knows, is like an endocrine organ, it modifies things, it reacts to aldosterone. We have no idea what the whole, it's cortex (indiscernible). So I think that's an easier

way to go, but that's a little, you know, different. Okay, it's a thought.

DR. THOMAS: Dr. David Cooke?

DR. COOKE: The only brief comment I would make regarding the fourth bullet point is this issue of predicting the ultimate cardiovascular outcome is complicated. There is this relatively modest increase in LDL, but it's potentially balanced by some beneficial effects of the decreased blood pressure, decreased weight, rising HDL.

So I would agree that ultimately we have to wait and see. But currently, without a concerning signal, I think I'm not bothered by the cardiovascular risks at this time.

DR. THOMAS: Dr. Lewis?

DR. LEWIS: I think you must have read my mind, because I don't remember putting my hand up. But I do have a question for the FDA, because I'm not sure I still understand the answer to it.

What are the precautions that have been taken to make sure that the people in CANVAS, once the drug is available, don't cross over to active drug? And

what are the agreements, if any, should the ultimate results of CANVAS either not be done, because you just can't get the results because too many people crossed over, or they're negative?

Will the drug -- I mean do you have an agreement about what would result in removing the drug from the market at that point?

DR. PARKS: There are a lot of questions in there. Now the first one you're touching on, that is a very, very complex issue. I'm not going to speak about CANVAS specifically; it's more of in general. What do you do with these ongoing cardiovascular outcomes trial where, you know, we're starting to see more of the agency considering regulatory decisions based on interim data, and how to protect the integrity of that ongoing portion.

And there are a lot of things that are being discussed with drug companies, within the agency, with our legal folks. The issue here is a matter of agency having to be transparent in our decision on whether a product has been deemed safe and effective for how we intend to label it, but at the same time, understanding

that sometimes the need to be transparent to the public may actually also affect our ability, the public's ability, the scientific community's ability, to be able to continue to get very good data.

These studies are going to be required post-marketing studies. So to that extent, that's where we have the regulatory teeth to ensure that they get us that information. I mean if they don't get that information because of complacency or whatever on a company's part, then there are penalties that can be applied.

If it's a matter of that there's been some impact, negative impact on the conduct of the trial because people have some erroneous preconceived notion on a limited amount of information, that is going to be problematic.

So these are issues -- I don't think we can resolve it here today, but if I can provide some reassurance to the panel member, these are active, ongoing discussions within the agency. Anywhere from, you know limiting the amount of information that can be provided at the time that we make a decision, or being

fully transparent and sharing all the information but coming down very strongly with any of our decision memos saying you know one should not make any definitive conclusions on the overall cardiovascular safety of this product to start impacting how one behaves, or how one conducts a clinical trial. That may do it. This is very much uncharted territory.

And then, at the end of the day, one also has to remember that-- you know the issue is that while the information may be -- the end results may be shared, if the trial is still indeed double-blinded and controlled, is that a level of reassurance? So I don't know if I've answered your question. The only thing I can say is that we have been thinking about this significantly.

DR. LEWIS: Well I guess maybe the company knows the answer to it, too. Like I'm wondering -- like say it got approved today. That means that -- it doesn't mean that tomorrow someone could go to a pharmacy and get this medicine.

So there is this time lag that's sort of inevitable while they do all the stuff they have to do

and market and whatever. How close will be to the end of the CANVAS trial before a patient could go to a pharmacy and get this drug? Do we know that?

DR. THOMAS: Sponsor?

DR. STEIN: So just as a note, the trial remains double-blinded. And we are very carefully tracking the discontinuation rate, which of late has come down substantially. We're making tremendous efforts to try to avoid losing subjects.

Obviously, we don't anticipate that we would have any meaningful loss of subjects based upon the release of the information, but we'll track that and obviously have to discuss with the agency the implications if that were to occur. But presently the current discontinuation rate accruing is quite small. And again the trial remains double-blinded.

With regard to the time frame, the trial had a prespecified analysis which we've conducted in January. The next prespecified analysis would be -- we expect to be in 2015, based upon the current accrual of events with 500 events.

The trial will continue at least to that time

point, and then would potentially end at that point if the next step was met, which is to demonstrate the 1.3 upper bound.

DR. THOMAS: Dr. Kaul and then Dr. Rasmussen.

DR. KAUL: You know I just wanted to respond to Dr. Parks' statement. I agree with everything you said. But enrolling in a trial with the fore knowledge that the drug has already been approved is one thing. And enrolling in a trial where the drug is not approved and then you find out that there is a suggestion of benefit, it's very tempting for the patients to cross over to the, quote unquote, beneficial drug. And I think we should not underestimate the impact it will have on what the sponsor and the agency is trying to do is rule out unacceptable cardiovascular risk.

DR. THOMAS: Dr. Rasmussen?

DR. RASMUSSEN: I just wanted to make sure that we all understand that without knowing details of the protocol, I'm fairly certain that it's prespecified that patients are not allowed to choose other SGLT2s, or, if it was approved, canagliflozin.

DR. STEIN: That's correct.

DR. THOMAS: Can you use the microphone please.

DR. STEIN: Just to be clear, it remains double- blinded and there's no opportunity for patients to switch from one treatment to another. There's no allowance for other SGLT2 inhibitors. Patients may be treated, or expect to be treated, maximally to standard of care in this trial.

Maximal glycemic control on top of canagliflozin or the match to placebo, and of course aggressive other management of cardiovascular endpoints. But there is no opportunity for patients to add an SGLT2 inhibitor. If they were to take prescribed canagliflozin or prescribed any other agent, they would, in that class, they would have to be discontinued.

DR. THOMAS: Ms. Killion?

MS. KILLION: Yeah, I just wanted to respond also to Dr. Parks' comments. The, well that's not the word I want to use -- the adoption of a CV risk assessment for a drug, for diabetic drugs, it makes for a very complex world when it comes to drug approvals.

And as a patient, it's been a concern of mine for some time that, you know that this is -- that we have to be very careful not to overburden the research and development process because we all know that we need new and better drugs for diabetics.

And if we hold out the approval of drugs until the conclusion of long-term cardiac risk assessments, that's going to stall and it's going to chill development, and we can't have that as a diabetic population.

So, I have empathy for the FDA, and you're trying to balance this and to work with the sponsors to make sure that these issues do not adversely impact patients in an overabundance of caution. But you know, that said, we have to be safe, but we also have to be reasonable and serve the needs of patients.

DR. THOMAS: Dr. Hiatt? Dr. Proschan?

DR. PROSCHAN: I just didn't quite understand that last statement about discontinuing patients who take something else. I mean we don't usually do that in clinical trials.

DR. THOMAS: So if the sponsor just wants to

clarify that.

DR. STEIN: I was just indicating that we don't allow patients to take those agents. We haven't had, and we don't expect to see any of that occurring during the trial. We've been very aggressive at having the investigators maintain patients in this trial, and to continue to obtain follow up on the patients.

And so what I was saying is that we don't allow -- the protocol specifies that they would not be allowed to take another agent. I don't expect that to be an issue at all in the trial.

DR. KAUL: You know, for intention-to-treat analysis is going to be impacted. Your protocol, per protocol analysis is going to be preserved if you do what you just said. But the intention to treat analysis is going to be -- I mean there are numerous examples.

Just a recent example that comes to mind is a chemo therapeutic agent that was approved for renal cell carcinoma. I think it was a multikinase inhibitor, sorafenib, approved on the basis of a surrogate endpoint. And under subpart H, the patients

then crossed over. And when the final results came out, there was no evidence of any benefit. So there are many other examples. So one has to preserve the integrity of the dataset.

And you know, I mean you have to weigh the pros and the cons. As you correctly mentioned, you don't want to overburden the development and the introduction of these potentially beneficial drugs. But there's a price to be paid and one has to be aware of that. How can you minimize that error?

DR. THOMAS: Dr. Knowler?

DR. KNOWLER: I'll just add to this comment. Once a drug is approved, you either -- I mean if you say you will not allow anyone to go on that drug, that simply means you're abandoning the intention to treat principle, which is not good.

You can't stop someone from getting the drug from their doctor. You cannot provide it yourself, but you can't stop them from getting it outside.

DR. THOMAS: Any additional comments? Otherwise, I'll -- Dr. Rasmussen?

DR. RASMUSSEN: I'll just comment to that.

Fortunately, within the diabetes field, there are a lot of other alternatives. So it's fairly easy, in a protocol, to prespecify, please choose something else for the integrity of the trial.

DR. THOMAS: All right, I will try and summarize this, and probably I'll have a few corrections from the panel.

Overall, the concern about the proportional hazards model seems to be less. For one reason is that there have been some sensitivity analysis that have been done and additional data analysis that suggests that it seems to be reliable enough to make some interpretation of what's happening.

The data seems to be fairly believable and actually has a value of less than 1.3, and really we're looking at a value of 1.8 for this initial analysis. If you look at the concerns about the 30-day changes in risk, it's not sure what's really happening there because there are a lot of changes that are going on, that have been mentioned throughout the day, including vascular changes such as dehydration.

There are changes in electrolytes. And none

of these have been specifically linked to why there might be this early increase in events in the treatment group, but there's an uneasiness from some of the panel members that maybe something is going on.

However, this was not a prespecified analysis. And if you were to do this -- if you were to prespecify it, you'd have a greater chance of actually making interpretations of this data if it's useful, and it wasn't significant.

If you were to do the data analysis, you could potentially take any clinical trial, look through the data, and pick a 30-day or 60-day period where there might be differences in the outcome, whether it's favorable for the agent or negative for the agent. So it's probably not a good way of looking at the data.

The concern of course is in the first 30 days. As we know from the surgical literature, there are many examples of surgical procedures, carotid endarterectomises, gastric bypass surgery, where there's a short-term increase in mortality, but there's a long- term benefit. And what we don't know is that in the future, is there really a short-term increase in

mortality?

And I'm going to add this in, is there a specific subgroup, which is not identifiable at this time, that's at highest risk for this? Or is this just a red herring and we'll see a long-term benefit? That probably still has something to be answered from a long- term trial.

What's the risk of the stroke issue? There's a couple of opinions that were floated by the panel. One is that the other components of MACE-plus were favorable. The point estimate was less than one. The hazard ratios were also within guidance. So people, even though there's an increased stroke confidence intervals, felt a little more reassured that the other ones are going in the right direction.

I will just throw out a comment that stroke is actually kind of concerning in the sense that we make an assumption that MACE and MACE-plus had all the components going in the same direction. And it's clear there are several clinical trials where that is not the case. The one, of course, I'm most familiar with is the one I was part of, which was the ACCORD trial.

In the ACCORD blood pressure trial, the primary outcome was not significant, but the prespecified secondary outcome that looked at stroke and the other MACE components, stroke was actually decreased in the intensively treated blood pressure arm versus the other components were neutral or tended to -- actually had no benefit.

So, in that case, it was a favorable benefit on stroke, though it was a secondary endpoint, and the primary endpoint was not there. So I'm not reassured that they're always going in the same direction. And ACCORD is not the only trial where stroke goes in a different direction than the other components. So I think that's something that needs to be looked at further.

There's a concern about the trial design. Because there's the initial evaluation of 200 events, that could have an impact. I'll discuss that a little further. But the specific one that's related to this is the addition of a type one error.

Because there are two sets of outcomes in this trial, there's an outcome for benefit that looks

at MACE, and there's an outcome for safety that looks at MACE- plus, how do you handle that when you have two sets of outcomes in the same trial, in terms of the type one error? And that's one that's going to be potentially difficult to reconcile.

When you look at other clinically relevant markers, blood pressure, weight change and low density cholesterol levels, we tend to feel that weight change is of significant importance. I'll add one more comment, the weight change seen in this drug, I would be hard pressed to see if that would actually have an outcome measure.

We know from recent data, though we haven't seen the published data, the Look AHEAD study actually had significantly more weight loss in the diabetic population with no apparent primary outcome impact. That data is not published, that was just in a press release, so that was a much more -- that was a greater amount of weight loss, five percent, than you saw with this agent.

So I think this level of weight loss, it's better than gaining weight, but I don't think we can

make any long-term outcomes, or predictions of how that's useful.

In terms of blood pressure, in terms of blood pressure medications, all the blood pressure medications tend to be reviewed by the cardio renal panel. They have effects on lowering blood pressure tend to have outcomes that are beneficial. This is a very unique way of lowering blood pressure.

It's not really attacking a pathophysiology mechanism; it's really related to osmotic diuresis. And I'm not sure that just lowering blood pressure by one of these mechanisms that's not in the pathophysiology of hypertension will you see the long-term benefit.

For LDL cholesterol, and other markers that are related to that, it's going in the wrong direction of what we would like. We would like it to actually go in the opposite direction, or potentially be neutral. And we've seen this before in the class of rosiglitazone where there is also an increase in LDL that was relatively small but it was in the wrong direction.

And so I think long-term studies are going to really have to look at what that impact of that small elevation of LDL cholesterol, a slightly smaller elevation of LDL particle size, means in terms of the long-term outcomes.

Finally, there's these issues about the trial design. You know there's a competing interest here. There's the interest for patients that agents that are efficacious, and potentially that could be useful to them, are available to them in a reasonable time. And then there's the balance of safety to protect these same patients.

One way that's being addressed, and it's still under a lot of discussion with the FDA, is to do this two-step model within the same trial, to look at preliminary events for initial evaluation, and then look at later events in the trial to see if it's safer at the lower 1.3 estimate.

There's some questions about whether this is the right way of doing the trial approach, and questions about the integrity of the trial. Not questions of how it's being handled from the sponsor.

Of course, they're keeping it double-blind and doing everything else possible, but in terms of intention to treat analysis and other related matters.

The benefit though is potentially the drugs would get to market sooner. And, if you had to do two separate trials, you would have a much later starting point for the second cardiovascular trial, so you wouldn't get the data sooner after approval. Because this trial's ongoing, you should have the data much sooner after approval, if the drug is approved, to make a decision about the long-term cardiovascular safety.

And I just want to add one last comment related to what Dr. Capuzzi mentioned is because this is a osmotic mechanism, there may be other factors that are being impacted that weren't really addressed or thought about.

And the ones that I've spent some of my career studying, aldosterone and renin-angiotensin is, you know, this osmotic diuresis, we really don't know what it's having on the renin-angiotensin aldosterone system directly.

And we know, in the cholesterol-lowering

world, there have been several agents that have had a negative cardiovascular mortality impact and there's been postulation that this may be involved with alternations to the renin-angiotensin aldosterone system. So that might be something further to look at in these ongoing trials in terms of a safety signal.

Any additions or comments or -- Dr. Proschan?

DR. PROSCHAN: A couple of things. With regard to the 30-day analysis, one thing that I think, you know, should be made clear is that it's really difficult. The FDA did absolutely the right thing in trying to look at that and you know, statistics is as much an art as it is a science. And so you have to do these kinds of things. I think they did absolutely the right thing; it's just very hard to interpret.

The other thing, with regard to the interim analysis, I think that this would have been a huge issue if the FDA had said, if you want to you can use the interim analysis, if you don't want to use that, you don't have to use that; maybe you could wait another six months and use the data then.

Then there'd be a huge issue with the interim

analysis because the results would be very biased if they could pick and choose, do we want to include this or not include this? But I don't think that was the case here. I think that was the plan all along to use those data. So I don't think that is as big an issue as if it happened the way I described.

DR. THOMAS: Any other corrections or additions? Okay. At this time, we're going to take a 10 minute break. I will remind the panel members that there should be no discussion of the topic while you're on this break. And we will reconvene at 3:45.

(A recess was taken.)

DR. THOMAS: We're going to start with question four, which is the first of the two voting questions. 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've 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 be then displayed on the screen. Mr. Briggs will read the vote from the screen into the record.

Next, we will go around the room and each individual voted will state their name and their vote into the record. And you can also state a reason why you voted as you did, if you want to.

And I'd just add, and the FDA greatly appreciates the comment of why you voted, regardless of what your vote was. We will continue in the same manner until all questions have been answered or discussed.

I'm going to read question four. Dr. Gregg? Yes. If you can turn your mic on.

DR. GREGG: So to clarify, we have two separate voting questions?

DR. THOMAS: Yes, we have two separate voting questions. This one, which I'll read out. And then we have an additional voting question, question number five. Any other questions before I read question number four? Okay.

In accordance with FDA's guidance for industry titled, Diabetes Mellitus -- Evaluating CV Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes, at the time of NDA submission, all applicants are to compare the incidence of important cardiovascular events occurring with their investigational agent to the incidence of the same types of events occurring with the control group, to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8.

Based on the data submitted, and considering the points of discussion in question three, do you have any concern regarding a conclusion that a risk margin of 1.8 has been excluded for canagliflozin? If you voted yes to question number four, remember to please provide your rationale when we go around the room. If you voted no to question number four, please provide your rationale. Dr. Brittain?

DR. BRITTAIN: Yeah, I just wanted to get a clarification because it seemed like this question is asked in a way that's kind of backwards to the way we

usually ask, they ask. A is -- voting yes, means I have concerns; voting no, means I do not have concerns. Is that right? Okay.

DR. THOMAS: So voting, so just to clarify, so voting yes means you have concerns?

DR. PARKS: Let's just read the question. Do you have any concerns regarding a conclusion that risk margin 1.8 has been excluded for canagliflozin? Yes or no? Do you have any concern? Yes, I have concern. No, I do not have a concern. Does that help?

DR. THOMAS: Dr. Lewis, you had -- you just turned your mic on. You had a question? Can you turn your mic on?

DR. LEWIS: Does this question very narrowly address this whole issue of the proportionality thing, and yes, you buy that it's okay or it's not? Is that what this question is? And then which one of these, if you think that yeah, it all worked out, I believe what Dr. Brittain said about the proportionality thing is cool, then you would vote B? I'm just trying to -- I actually don't understand what I'm supposed to do.

DR. THOMAS: Dr. Kaul?

DR. KAUL: I mean the way it is phrased, the answer is always going to be yes because any concern -- all of us have some concern. So I mean I'd like to get a better understanding of -- a major concern.

DR. PARKS: Yes. I think that's where the rationale part will be very, very critical. I mean it's conceivable that you have heard all the discussions this morning, this afternoon, and you're convinced that, you know all the items that were discussed under point three have satisfactorily been addressed, conceivable that you have no concern.

But if you have any lingering, then I don't want to in any way bias your vote here, but if you have any lingering concern, you can say vote yes, and explain what that concern is. It may be a minor or a major concern. But I just want to make sure -- is that all right with you or do you want to make it more simple? Yes or no?

DR. LEWIS: Are you still just wanting us to address the narrow question of the 1.8 issue and proportionality? Because the next question seems to get more broad concerns. Or are you wanting to ask --

are you trying to ask us, do we have any concerns about cardiovascular stuff?

DR. ROSEBRAUGH: Just a minute. So I think what we're trying to get at with this question is, unlike question five, which is decisional, this question is more just to help us get a sense of your comfort with the certainty of the cardiovascular data that we've been provided.

So I wouldn't view this, if you answer one way or the other, that's made the decision on whether the drug should be marketed, it's more to help us because we have been struggling with this 30-day issue and some of the other issues, so we just want to get a sense of how concerned you are about these issues. And I don't -- were you going to read your statement again, your opening statement? Was there something to help?

DR. GUETTIER: Yes, if I can reread the opening remarks I made this morning about this question. So for this question we want you to weigh the totality of the evidence surrounding cardiovascular safety, including the issues raised in discussion point three, so it's not just limited to the proportionality

hazard, to tell us whether you have concerns in concluding that a cardiovascular risk margin of 1.8 has truly been excluded for canagliflozin.

So again, it's the totality of the cardiovascular safety data. And it basically follows from the discussion points for question, for discussion point three, the bullet points for discussion point three.

DR. THOMAS: Dr. Proschan?

DR. PROSCHAN: So I take it from that, that you don't intend to change, to modify concerns to say serious concerns or -- you want it just as it is?

DR. ROSEBRAUGH: Yeah. And I think you can modify, in your response, when you answer us, whether you think it's serious or not.

DR. THOMAS: Okay. So I think the upshot is your discussion will be very helpful to the FDA. Okay, we'll go on then. If there's no further discussion on this question, we will not begin the voting process.

Please press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to vote. Please press the button firmly.

After you've made your selection, the light may continue to flash. If you're unsure of your vote, or you wish to change your vote, please press the corresponding button again. You can vote now.

DR. BRIGGS: The vote is eight yes, seven no, zero abstentions.

DR. THOMAS: We'll now go around the room. And just remember to state your name for the record, your vote and your rationale for your vote. And we'll start with, on my left, Dr. Hiatt.

DR. HIATT: Well yes, I do have residual concerns. In terms of taking that question literally, there's no doubt that the upper bound of 1.28, .29 is way below 1.8. Also, it's unlikely that that bound will get to 1.8 at the conclusion of the cardiovascular outcomes trial, but it could go above 1.3.

And so as -- not to dwell on sort of some earlier comments, but the idea that there's an early risk signal likely won't change, because the study's recruited. The probability of a late risk signal, because of the LDL effects, may be impactful.

But here's where I sort of wind up on this.

If this outcomes trial is run to completion, from 200 events to 500 events, and the point estimate is still below 1.0, and the upper bound is still below 1.3, then I think that significantly mitigates this early risk concern. That's kind of -- I think that's sort of the thing that's most concerning, because that's in front of us, right.

And so if that's still going to be there, which is likely going to be there, but overall, you see that these results that we currently are looking at, they just remain unchanged. And the point estimate is still less than 1.0 and the upper bound is less than 1.3, then I think you can say to a patient, look you take this drug, there may be some imbalances early on, but overall you're going to be fine.

And so therefore I think the answer to these lingering concerns is really in the totality of the data, which we don't have yet. And that's my lingering concern.

DR. KNOWLER: Well I basically have no concern -

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DR. THOMAS: Dr. Knowler, if you could introduce yourself and your vote.

DR. KNOWLER: Yes, William Knowler. I voted yes, that I have a concern. I'm actually quite satisfied with the data that we have seen, that the drug is safe in terms of cardiovascular events. But as I stated in earlier discussions, I cannot have all my concerns allayed by data which, for the most part, only go for about a year, or some for a little bit longer. I think to be perfectly satisfied, I need to see longer term data, especially in view of the lipid risk factors.

DR. GREGG: I'm Ed Gregg. I voted yes. I actually do not have concern about the overall cardiovascular disease risk ratio here, and was not actually that concerned about the first 30 days as I saw that due to a reliability and probably due to chance.

Where I had some concern, to answer the question more directly, and particularly related to the 1.8, was with stroke, because that was a more general, from a generalized analysis over the entire length. So

that would be where I would say some concern.

DR. CAPUZZI: Yes, I voted yes. And --

DR. THOMAS: Dr. Capuzzi, if you could just state your name.

DR. CAPUZZI: Oh, I'm sorry. David Capuzzi is my name. Just a couple of points, part of the issue here has been this huge volume of material that just flows in incoherent, well not incoherent, but in a diffuse way. It's very hard to follow the reasoning of it.

However, I mentioned the lipid data, that's a concern. I'm not sure it would be a reasonable concern if people knew ahead of it, prospectively while they were treating the patient and got everything in order. This is something that just popped up, and it wasn't explained well in the text. But that is an issue. That is an issue.

And you know, and that doesn't mean that -- the other -- but one of the things that I'm concerned about is there are international companies running analogs of this and they're not part of the United States. On the other hand I don't like to see that

happen because I don't know that there's the same care and follow up with people like that, and with other nations in other words.

But, so I really have mixed feelings and I just hope that this could be straightened out. That's my really, my only rationale. And this was very diffusely written and hard to read. But the issue, as I understand it, and I still have some edginess because of the negativity shown in the results. And let's see, the next question, provide your rationale. Oh, I'm sorry.

DR. THOMAS: Well we'll wait until the next question after the vote. Dr. Brittain?

DR. BRITTAIN: Erica Brittain. I voted no. Of course I have at least some concerns, so I did not take the question literally. But I voted no, even though there are certainly some uncertainties about the cardiovascular risk with respect to the first 30 days, and certainly not much information about long-term follow up.

But with respect to the prespecified 1.8 benchmark, and that benchmark was, I assume,

established with the understanding that the data were going to be fairly short-term, I think the evidence is quite clear. That said, it's critical that the CANVAS trial be completed and in such a way that it will provide meaningful long-term data.

DR. THOMAS: Abraham Thomas. I voted no. I think overall the data that was presented actually support that they're well under the 1.8 threshold. And there's nothing that was really presented that would give me the ability to say we were -- something should be altered to the program or the study.

However, that doesn't mean that there aren't concerns. The three that I would bring up are, the most concerning for me is actually the stroke, because it's in the wrong direction and I'm not reassured the other factors, because they're going in the right direction, are enough to say it's safe. But there's no way of answering that question without more data, and so the rest of the trial is going to hopefully add to that and see if it's a real concern or not.

The LDL cholesterol one of course to me is also a concern, and that really also needs longer term

data than an interim analysis that was used here because you need probably several years to see that impact of LDL cholesterol.

And the last one, which I'm not too concerned right now, is the 30-day analysis, just because it's quite possible that's chance. However, that shouldn't be neglected in the future analysis and we'll see if that's a real factor or not. We may actually never get that answer, but at least hopefully with more data we'll be reassured.

DR. COOKE: David Cooke. I voted no. Placing the weight on the prespecified outcome, cardiovascular outcome that was well below 1.8, I'm comfortable that they showed that very easily. I think I agree that the post hoc analysis that identified the early cardiovascular events and the strokes is something to be considerate of, to think about. And certainly I would agree that the stroke outcome is of most interest, but that should come out with longer term data, but otherwise I'm comfortable with where we are now.

MS. KILLION: I'm Rebecca Killion and I voted

no. I'm not going to reiterate what's been better said by my other colleagues at the table, but I will now make a statement with at least five qualifying elements to it.

At this stage, and with the information that we have now available, I have no overriding concerns about the CV risk, but I think that the story continues to unfold, and more will be revealed as the study continues and we need to stay on top of that.

DR. KAUL: Sanjay Kaul. I voted no. I think the concerns that I have with regard to the cardiovascular database I've already enunciated. It was interesting to learn that the guidance, the FDA's guidance is a dynamic document. It's not a rule, it's only a guideline and it's interesting to see how it is evolving, or will evolve in the future with this precedent-setting drug.

The couple of things that I would like the sponsor to do is to sort of clarify, or better characterize the endpoints in order to understand what the clinical impact is on the patient. And I'm sure all the data is already available there, you just had

to go back and look at it, and maybe it would even be a post hoc adjudication of a Rankin score and see what the impact is.

What is the relevance of this unstable angina leading to hospitalization? Does that translate into something meaningful or is it just one of those soft endpoints that does nothing but add noise to it and sort of shift the upper bounds towards the null?

And this early hazard, it's difficult to make much of it. I'm not willing to completely dismiss it. I think the protocol needs to be amended, if it hasn't already been done, to capture the early events because the first patient visit was at six weeks, and the events cluster around day 30.

It's quite possible that you may have failed to capture some of the events, clinical or laboratory events, with all these events occurring beyond the first time period of assessment.

I have concerns about the fact that the dataset is only one year. I would like for a chronic disease --

DR. THOMAS: Dr. Kaul, sorry to interrupt

you, but could you repeat what you said when you turned away from the microphone, or come close to it for the transcriptionist? Thank you.

DR. KAUL: Okay. I'm so sorry, I was addressing them. So my name is Sanjay Kaul. I voted no, but I do have concerns. The first concern I have is that the exposure, the period of exposure is rather limited. For a chronic disease, I would at least expect to see a longer follow up. And I think the -- it's reassuring to know that the longer follow up will be coming.

I would like the sponsor to go back and better characterize the events, specifically whether the strokes were disabling or not. Characterize the type of MIs. Were they clinically uncertain biomarker elevation events, periprocedural events, or were they real spontaneous Q-wave myocardial infarctions?

I would also like them to sort of amend the protocol, if they haven't already done that, to assess the patients, the first visit earlier, in order to capture some of the early hazard, if it is real. And that's it.

DR. COOK: Nakela Cook. And I voted yes. And I voted yes predominately because I still do have some concerns. And I think that they've been voiced here, and some concerns that people had the same ones and voted no for.

So I think the issue for me was really around stroke and whether or not that increased hazard is really real, and whether or not time would actually take that above the 1.8, in addition to the increased LDL levels.

And so kind of trying to figure out if longer follow up with those two issues would actually make me feel confident that we were at 1.8, and I didn't think so with my vote.

DR. PROSCHAN: I'm Michael Proschan and I voted no. I think, when you look at overall cardiovascular events, to me there's no question that they've shown that it's under 1.8.

With respect to, you know one component, namely stroke, I still have some questions about that. It's hard to feel confident that, you know that there's no increased risk given that confidence interval. But

for overall cardiovascular, I think they've demonstrated what they needed to.

And so, and I can't say whether this stroke thing is real or not. With regard to the 30-day events, I can't be sure that that's not real either, but I think it's -- I would -- I am betting that that is the play of chance.

DR. SAVAGE: I'm Peter Savage and I voted no, for many of the same reasons that have already been mentioned. I thought that in this case the, for overall cardiovascular disease risk, it looked to me as if they were very likely to have achieved the goal for meeting what the conditions were.

DR. MALARKEY: I'm Dave Malarkey and I voted yes. I was confident that the risk ratio of 1.8 wasn't met, but my biggest concern is the angst that's been shown by my fellow panelists who know more than I, and hearing that the data's not complete yet.

DR. LEWIS: Actually I'm not sure I can remember which is yes or no even now. But it sounds like we're all saying the same thing, whether we voted yes or no. But I actually am not worried about the

first --

DR. THOMAS: Dr. Lewis, if you could just state your name and your vote.

DR. LEWIS: Oh, Julia Lewis. I'm not worried about the --

DR. THOMAS: And your vote.

DR. LEWIS: Oh, my vote was yes. So I wasn't -- I actually am not concerned about the MACE and the 1.8 and the first 30 days or the stroke. I think, you know, I give them all that. I think the numbers, overall, look good. It's a composite. I'm okay with all that.

My residual concern remains that the number of people who have had sufficient follow up to assess the cardiovascular risk of LDL cholesterol being elevated, slightly worse renal function, higher phosphorus', I mean there are several things that could impact, and it might take longer. Even though a lot of people have gotten this drug, many of them it's for a very short time. So that was my residual concern.

DR. PALEVSKY: Paul Palevsky. I voted yes. I voted yes very narrowly based on the any in there, of

any concerns, same issues that I think everyone else has raised, particularly the stroke.

I suspect that that's not going to play out, but there's some concern there. I suspect that the 30-day data is a statistical aberration, but there is some concern there. So because of the word any, I voted yes.

DR. THOMAS: Dr. Rasmussen, would you want to comment on this or do you want to save your comments at the end of -- up to you.

DR. RASMUSSEN: I'll add a few comments here as it pertains to the CV risk assessment. The sponsor has conducted the largest program for a single compound in diabetes and collected 200 CV events, much more than we're used to seeing.

They've conducted the prespecified analysis according to the agreement they had with the agency, and came out with point estimates below 1.0 and with upper bounds less than 1.3.

The spirit of the guidance is to exclude an excess risk of 80 percent. So that's at least what's been discussed so far. And I think even though there

are some lingering concerns, that we'll have an opportunity to address down the line with the accrual of more data. I think they've lived up to what they intended to do.

DR. THOMAS: Thank you. We'll now move on to a voting question, which is question number five. Dr. Lewis?

DR. LEWIS: I have a question about this question, which I guess I know the answer, but --

DR. THOMAS: Can I just have you wait until I read the question then I'm happy to take that.

DR. LEWIS: Yeah. Okay. Sorry.

DR. THOMAS: Okay. Based on the information included in the briefing materials and presentations today, has the applicant provided sufficient efficacy and safety data to support marketing of canagliflozin for the treatment of type 2 diabetes mellitus?

A, if you voted yes to question number five, please provide your rationale and whether you recommend any additional studies post-approval. B, if you voted no to question number five, please provide your rationale and discuss what additional data are

necessary to potentially support approval. Dr. Lewis?

DR. LEWIS: The agency, and actually the sponsor, both gave us much information about the low GFR group. And I've already expressed my concern that it may not be in their best benefit risk issue to receive this drug.

This question does not allow -- if I vote yes, or if I vote -- yeah, if I vote yes, it goes to them as well. You didn't let us carve them out. Was that by intent or?

DR. PARKS: That was intentional. I think that if that is really a critical point for you. That may be a reason why you want to vote yes or no. And again, it goes to the rationale explaining why that should be.

DR. THOMAS: Dr. Knowler?

DR. KNOWLER: Yeah, I have a somewhat similar concern. I raised the question this morning about whether you were requesting approval to use the drug as an add-on to other medical therapy to diabetes, or as monotherapy, and again, this question doesn't address that.

But my own view, I might as well state it right now, is I see reasons to consider this as add-on therapy, but I see no reason to consider it as initial therapy when there have been no comparisons made with metformin, which is the standard initial therapy. So given that, I'm not quite sure how you would want me to vote.

DR. GUETTIER: So I think you know the indication for all anti-diabetic agent is a broad indication. A few years back we used to give indication as monotherapy, add-on to metformin therapy, and that has been done away. So we have a simplified indication for diabetes.

The results of all of the Phase III trials are in the label, under the clinical studies section. And although we don't specify anything, the data is there for physicians to look at.

DR. KNOWLER: So if I understand, you're saying the FDA now will not approve a drug for certain patients but not for others. It's either all or nothing?

DR. GUETTIER: The broad indication is

commensurate with the studies that were done in the Phase III program. So if the sponsor has studied different clinical scenarios, that will be in the label. If the sponsor has not studied other specific clinical scenarios, then there will be either a limitation of use in the label, saying that it's not appropriate for a specific clinical use scenario.

But if this particular sponsor has studied a monotherapy indication, the study for the monotherapy arm will be in the label, and physicians will be able to decide whether or not they want to use this as first-line therapy or as second-line therapy. But the FDA doesn't have any say in that.

DR. THOMAS: Is that enough, Dr. Knowler to vote?

DR. KNOWLER: Well I think you've answered my question, although I don't like the answer. I'm not sure what else we can do about it.

DR. PARKS: And I don't know if this is going to help you in determining how to vote, but if you think -- so what you're heard from Dr. Guettier here is that how the clinical development program has been

structured, the Phase III trials will be, if this product gets approved, will be described under the clinical studies section of the label, so that prescribers can be informed on the efficacy and safety in the many different uses of the anti-diabetic product.

Now, if you think that there is a method of use that has not been studied, and you think that it's a really critical method for use that you think that there's a large gap of knowledge there, then that might influence your decision.

If you think that there's a method of use that's missing, but not having it in the label, or as Dr. Guettier said, a limitations of use could still be helpful to the prescribing population where they can so oh, it hasn't been used here, I probably shouldn't use it, then that might also influence your vote. Does that help?

DR. THOMAS: If there's no further discussion on this question, we'll now begin the voting process. Please press the button on your microphone that corresponds to your vote. You have approximately 20

seconds to vote. Please press the button firmly.

After you've made your selection, the light may continue to flash. If you're unsure of your vote, or you wish to change your vote, please press the corresponding button again.

DR. BRIGGS: The vote is 10 yes, five no, zero abstentions.

DR. THOMAS: We'll start around the room to my left. Dr. Hiatt? Just a reminder, please state your name and your vote and then your rationale on how you voted yes or no.

DR. HIATT: William Hiatt. I voted no. Just to be brief, I think the cardiovascular risks have not been fully evaluated. And I think that they will be, hopefully it sounds like maybe it will take two years.

Though the sponsor did show some updated numbers on those events that I didn't know how you got there, if you weren't continuing to unblind the outcomes trial. But I would hope that these issues, residual issues I have, would be resolved at the completion of the outcomes trial.

DR. KNOWLER: William Knowler. I voted no

for the reasons I just described a few minutes ago. Basically I think the drug would be acceptable as add-on therapy in some patients, but for a general indication, including monotherapy, I cannot recommend it.

DR. GREGG: I'm Ed Gregg. I voted no. The risk benefit judgments are unfortunately subjective, and this one was particularly difficult. I found that we saw a diverse set of benefits here, but they were largely surrogate outcomes wherein the mechanism this novel could conceivably affect the long-term impact. And I found this clouded by the fact that the benefits were less in a large segment of the target population.

And we had a variety of lingering questions, ranging from bones and fractures, to renal function, to stroke, volume depletion. And so in the end, I found myself weighing a lot of maybe benefits versus a lot of maybe risks. And I would have felt I think -- perhaps my uncertainty would have been diminished if we had a full sample for two years. So that would be my recommendation.

Aside from the fact that when you have a lot

of -- a diverse set of benefits and risks like this, it would have been nice actually to see some data on function and quality of life and I didn't see that in the mix here.

DR. CAPUZZI: Yes, I voted no. It's not a negative no, it's a positive no. But at the same time, it's a tough decision and I think we're all thinking along the same lines. I just don't think there's enough data here. I think that it will come out just fine --

DR. THOMAS: Dr. Capuzzi?

DR. CAPUZZI: Yes?

DR. THOMAS: One, if you can state your name. And two, just --

DR. CAPUZZI: Well, my name, David Capuzzi.

DR. THOMAS: And just to make sure, you said you voted no but --

DR. CAPUZZI: I voted no and it's staying that way.

DR. THOMAS: No, no. You're listed as voting yes on the --

DR. CAPUZZI: Was it -- wait a minute, what

was the question? Oh, wait a minute. I'm sorry, wait a minute. Thanks a lot.

DR. THOMAS: While we do this. We'll come back to you while you're just clarifying if you need a moment to think about it. Dr. Brittain?

DR. BRITTAIN: Yeah, Erica Brittain. I voted yes. You know, I thought the efficacy results were very robust, even with some signs of superiority in the non- inferiority trials.

Yes, it is -- a primary endpoint is a surrogate endpoint, and that's not, you know obviously that has problems, but it was, again it was and agreed upon primary endpoint, and the results were very strong on that.

And it seemed, the results seemed strong enough to outweigh some lingering safety issues, the renal issues, the bone issues. And then there's this slightly confusing cardiovascular picture, but actually I think the cardiovascular picture's fairly promising, although as we said before, it will be very important to get the long-term data from the CANVAS trial.

I did also want to concur with others that

the risk benefit trade-off for the renal impaired population, however it gets defined, clearly is less clear cut.

DR. THOMAS: Abraham Thomas. I voted yes. There are definitely benefits to this drug. There are risks. I still have concerns, as many others do. One thing I'm reassured about is, you know MACE, the reason we use MACE is to accumulate enough events.

Each individual component, it's unlikely you'll enough events, so even with the issue of stroke, you may not see enough events during the trial to be able to make a final decision about safety or not.

But I'm reassured that in the past, in one of the over-the-counter obesity agents, the FDA was able to use epidemiologic and surveillance data to remove it from the market.

So I think one of the things that's important is in many of these areas, fractures, the cardiovascular risk, the long-term follow up should not be just the trial and specific trials addressing some of these issues, like bone safety, but really does have to involve registry data, surveillance data, HMO data

to pick up some of these factors that I think are really hard to identify in a trial no matter how large.

DR. COOKE: David Cooke. I voted yes. And again, I think the efficacy data were clear, at least in terms of the surrogate endpoint. I agree that ultimately a real outcome would be better.

But again, I think balancing the realistic expectations for investigations prior to approval, without putting excessive burden that would inhibit development and delivery of these medications to a very important needy population in terms of imperfect control currently.

And so although the risk data is incomplete at this point, I think it is sufficiently reassuring to justify the efficacy data and approval at this time.

MS. KILLION: I'm Rebecca Killion. I voted yes. I agree with everything Dr. Cooke just said. But as a patient, I have to say I found that this drug very encouraging from several points of view. One is, I think it particularly addresses concerns that patients have with respect to struggling with weight loss, which directly affects the progress of their disease, and the

concern that all diabetic patients have about hypoglycemia.

In addition, it improves the hemoglobin A1c, and it represents a step forward, progress, in that it's a new mechanism of action for a drug. So all of that's very encouraging from a patient perspective.

There are some concerns that I have. As I said previously, I think this story still is unfolding. But I think that, from a risk benefit analysis, every drug has risks and it's not appropriate for use in all populations, but I think that that will be able to be worked out. So from a patient point of view, this is very encouraging.

DR. KAUL: My name is Sanjay Kaul, and I voted yes, but with one caveat. I think the sponsor has shown that the benefit exceeds the risk in patients with normal or mildly impaired renal function. I do not believe that the benefit exceeds the risk in patients with moderately impaired renal function.

I think that patient population was underrepresented in this trial, and I think they need to enhance the evidence base, meaning do more trials

specifically enrolling patients at moderate risk, moderate renal impairment, because the hypoglycemic efficacy was significantly reduced in this patient population, and the adverse events were increased by two to four-fold.

Even though the ascertainment process was not prospectively prespecified, and it was not stringent, it may actually turn out to be worse. And so since half of the patients in the cardiovascular dataset have moderately impaired renal function that also applies to that dataset as well.

I have concerns about the cardiovascular assessment, which I've already enunciated prior. I think the FDA will have to ensure the issues regarding trial integrity. And that's it.

DR. COOK: Nakela Cook, and I voted no, and actually for similar reasons that Dr. Kaul just mentioned. I was concerned about the group with moderate renal impairment and not having the risk benefit ratio in the favor of benefit there outweighing risk.

I think that overrode my vote. I actually

even, though I had some concerns around cardiovascular risk, I felt like longer term follow up data would help us with that. I was more concerned about the moderate renal impairment group at this stage, with the data that we have currently.

DR. PROSCHAN: And I'm Michael Proschan. I voted yes. I felt like there was a lot of safety data, although you know it would be nice to have longer duration, five-year data for example. But I thought that there was substantially more safety data than in many diabetes drug trials.

I was also persuaded, obviously I'm not a clinician, but I was persuaded by the ones who said, you know who talked about the importance of having a new class that doesn't depend on insulin. And so I voted yes.

DR. SAVAGE: Peter Savage. I voted no. My main concern was also that the use in people with moderate renal disease might not be appropriate at this time with the data that's available. It seemed to me that the risk benefit ratio was different in that group and that I didn't feel comfortable, maybe because it's

not a field that I have as much expertise in, but I didn't feel comfortable that this wouldn't in some way actually damage the kidneys with long-term urinary tract infections and so forth.

So that I just felt that that tipped my vote from yes to no, because I think it could be useful in other parts of the diabetic population.

I guess there's two other brief things I'd like to mention. It was said that it would be useful in terms of avoiding the risk of hypoglycemia, but one thing that occurred to me, that wasn't mentioned at all today, is that amongst the elderly, the ability to recover from hypoglycemia is somewhat blunted.

And so they get sort of poorer glucagon responses and so forth, and therefore their glucose may come up more slowly. And if you've got something draining glucose out of the kidney at the same time, I don't know whether there's any extra danger of more prolonged hypoglycemia in older people. I think it's something that ought to be at least looked into.

And you know I agree also with Bill Knowler that it seems to me there was no evidence presented

here that would make me think that this would be a replacement for metformin unless you had someone who had a lot of GI symptoms that just couldn't take metformin.

But you know, that's not as much a -- that at least probably wouldn't be that harmful. But the kidney question I have concerns about.

DR. MALARKEY: I'm Dave Malarkey. I voted yes. I felt the benefits outweighed the risk in this situation. The relatively low risks in the animal studies were nicely done and supportive of mechanistic studies. I felt there's some uncertainty with the long- term effects that needs to be monitored closely.

DR. LEWIS: I'm Julia Lewis. I voted yes. And I guess my vote reflects the fact that I have great faith in my FDA colleagues. I know they listened to a long and I think a great discussion with my colleagues here at the table.

I would expect that the labeling would reflect our concerns in the low GFR group at the very least. And I would anticipate, and it sounds like you guys are really thinking about how to ensure that

CANVAS does get completed with sufficient events in a timely time.

And the burden should be on the company to do that, and if not, they get cut off or something. I mean, then I bet you they'll find a way to do it.

So, but I am sure you will think of a way to make that happen. And with those two caveats, I felt comfortable that they had succeeded in fulfilling what was the intent and agreement with you, and was a reasonable approach to preliminary approval for this drug.

DR. PALEVSKY: Paul Palevsky. I voted yes. Similar concerns that I think have been expressed, both for the need for post-approval cardiovascular data, and with concerns about the use of the agent in the patients with more advanced kidney disease, the Stage 3B, so eGFR of less than 45 group of patients.

DR. THOMAS: Dr. Capuzzi, if you want to read your name and your vote again, and your rationale?

DR. CAPUZZI: Yeah, could you just clarify, what was my first vote?

DR. THOMAS: Your -- you mean on question

four?

DR. CAPUZZI: No, my question that was at -- oh.

DR. THOMAS: The vote we just did was on question five, which was the approvability.

DR. CAPUZZI: Right.

DR. THOMAS: And you voted yes on that.

DR. CAPUZZI: Okay. All right. As I hear people, I'll leave it that way. But as I hear people that -- everybody has the same concerns and need for the sponsor to follow up with appropriate studies and safety issues. But I think it's a good opportunity, very good.

DR. THOMAS: And Dr. Rasmussen, even though you're not a voting member, if you have any final comments.

DR. RASMUSSEN: Just very briefly. I seem to say this every time, I mean this was not easy and I want to thank all of you for carefully deliberating both the benefits and the risks. The sponsor already has activities ongoing that hopefully will address these in a timely manner. So the agency has every

opportunity to work with the sponsor to come up with a good solution.

DR. THOMAS: Do you have any final comments from the FDA?

DR. PARKS: Yes, I'd like to thank all the committee members, the chairman, Dr. Thomas, also Caleb for helping us out today. This has been a very dynamic and thoughtful discussion on some very difficult issues, and so we'll very much take all your rationale, your discussion points to heart.

I'd also like to thank the company for their presentations and working with us, especially in the last couple weeks, in responding to our requests. And then finally I'd like to thank the FDA review team for a phenomenal job preparing for this advisory committee. And particularly to Dr. Jean-Marc Guettier for leading up this multidisciplinary review team. Thank you.

DR. THOMAS: I'd like to thank the sponsor and the FDA for their excellent presentations, the panelists for their spirited discussion and excellent questions, the open public hearing speakers for their valuable input, and the audience for their attention.

This meeting's adjourned. Thank you.

(Meeting adjourned at 4:36 p.m.)

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