

Capital Reporting Company  
Endocrinologic and Metabolic Drugs Advisory Committee Meeting 01-10-2013

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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  
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4 Abraham Thomas, MD, MPH, Acting Chair, EMDAC 12

5

7 Caleb D. Briggs, PharmD, Acting Designated

8 Federal Officer, EMDAC 16

9

11 Jean-Marc Guettier, MD, Diabetes Team Leader,  
12 Division of Metabolism and Endocrinology (DMEP)  
13 Office of Drug Evaluation (ODE-II)

14 Office of New Drugs (OND), CDER, FDA 20

15

17 Janssen Pharmaceuticals, Inc.

19 Jacqueline Coelln-Hough, RPh

20 Janssen Research & Development, LLC

21 Senior Director, Global Regulatory Affairs 26

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1 M E E T I N G R O S T E R

2

3 ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

4

5 Caleb D. Briggs, PharmD

6 Division of Advisory Committee and Consultant

7 Management Office of Executive Programs, CDER, FDA

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9 ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

10 MEMBERS (Voting)

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12 Erica H. Brittain, PhD

13 Mathematical Statistician, Biostatistics Research

14 Branch, National Institute of Allergy and Infectious

15 Diseases (NIAID), National Institutes of Health (NIH),

16 Bethesda, Maryland

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18 David M. Capuzzi, MD, PhD

19 Professor of Medicine and Biochemistry, Thomas

20 Jefferson University & Lankenau Institute for Medical

21 Research, Philadelphia, Pennsylvania

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1 ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

2 MEMBERS (Voting) (continued)

3

4 Edward W. Gregg, PhD

5 Chief, Epidemiology and Statistics Branch, Division of

6 Diabetes Translation, Centers for Disease Control and

7 Prevention (CDC)

8

9 ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

10 MEMBERS (Non-Voting)

11

12 Mads F. Rasmussen, MD, PhD

13 (Industry Representative)

14 Executive Director, Diabetes - Clinical Development and

15 Research, Clinical Development, Medical and Regulatory

16 Affairs, Novo Nordisk Inc., Princeton, New Jersey

17

18

19

20

21

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1 TEMPORARY MEMBERS (Voting)

2

3 Nakela Cook, MD, MPH, FACC

4 Clinical Medical Officer, Clinical Application and

5 Prevention Branch, National Heart, Lung, and Blood

6 Institute (NHLBI), NIH, Bethesda, Maryland

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8 David W. Cooke, MD

9 Associate Professor of Pediatrics, Division of

10 Pediatric Endocrinology, Director, Pediatric Endocrine

11 Fellowship Training Program, Johns Hopkins University

12 School of Medicine, Baltimore, Maryland

13

14 William R. Hiatt, MD, FACP

15 Professor of Medicine, Division of Cardiology,

16 University of Colorado School of Medicine, President,

17 Colorado Prevention Center (CPC) Clinical Research,

18 Aurora, Colorado

19

20

21

22

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1 TEMPORARY MEMBERS (Voting) (continued)

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3 Sanjay Kaul, MD

4 Director, Fellowship Training Program in Cardiovascular

5 Diseases, Cedars-Sinai Heart Institute, Professor,

6 David Geffen School of Medicine at UCLA, Division of

7 Cardiology, Cedar Sinai Medical Center, Los Angeles,

8 California

9

10 Rebecca Killion

11 (Patient Representative)

12 Washington, District of Columbia

13

14 William C. Knowler, MD, PhD, MPH

15 Chief, Diabetes Epidemiology and Clinical Research

16 Section, National Institute of Diabetes and Digestive

17 Kidney Diseases (NIDDK), NIH, Phoenix, Arizona

18

19 Julia B. Lewis, MD

20 Professor of Medicine, Department of Nephrology,

21 Vanderbilt University School of Medicine, Nashville,

22 Tennessee

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1 TEMPORARY MEMBERS (Voting) (cont.)

2

3 David E. Malarkey, DVM, PhD, DACVP

4 Head, National Toxicology Program Pathology Group,

5 cellular and Molecular Pathology Branch, National

6 Institute of Environmental Health Sciences (NIEHS),

7 NIH, Research Triangle Park, North Carolina

8

9 Paul M. Palevsky, MD

10 Chief, Renal Section, Veterans Affairs Pittsburgh

11 Healthcare System, Professor of Medicine and Clinical &

12 Translational Science, University of Pittsburgh School

13 of Medicine, Pittsburgh, Pennsylvania

14

15 Michael A. Proschan, PhD

16 Mathematical Statistician, Biostatistics Research

17 Branch, NIAID, NIH, Bethesda, Maryland

18

19 Peter J. Savage, MD

20 Senior Advisor to the Director, Divisions of Diabetes,

21 Endocrinology, & Metabolic Diseases (DDEMD), NIDDK,

22 NIH, Bethesda, Maryland

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1 TEMPORARY MEMBERS (Voting) (continued)

2

3 Abraham Thomas, MD, MPH, FACP

4 (Acting Chairperson)

5 Division Head, Endocrinology, Diabetes, Bone, and

6 Mineral Disorders, Henry Ford Hospital, Whitehouse

7 Chair of Endocrinology, Detroit, Michigan

8

9 FDA PARTICIPANTS (Non-Voting)

10

11 Curtis J. Rosebraugh, MD, MPH

12 Director, Office of Drug Evaluation II (ODE-II), Office

13 of New Drugs (OND), CDER, FDA

14

15 Jean-Marc Guettier, MDCM

16 Clinical Team Leader, DMEP, ODE-II, OND, CDER, FDA

17

18 Mat Soukup, PhD

19 Team Leader, Division of Biometrics 7, Office of

20 Biostatistics (OB), Office of Translational Sciences

21 (OTS), CDER, FDA

22

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1 FDA PARTICIPANTS (Non-Voting) (cont.)

2

3 Mary H. Parks, MD

4 Director, Division of Metabolism and Endocrinology

5 Products (DMEP), ODE-II, OND, CDER, FDA

6

7 Hyon (KC) Kwon, PharmD, MPH

8 Clinical Reviewer, DMEP, ODE-II, OND, CDER, FDA

9 Products (DMEP), ODE-II, OND, CDER, FDA

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1 P R O C E E D I N G S

2 Call to Order and Introduction of Committee

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 Group at the National Toxicology Program.

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

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

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

10 DR. THOMAS: For topics such as those being  
11 discussed at today's meeting, there are often a variety  
12 of opinions, some of which are quite strongly held.

13 Our goal is that today's meeting will be a  
14 fair and open forum for discussion of these issues and  
15 that individuals can express their views without  
16 interruption.

17 Thus, as a gentle reminder, individuals will  
18 be allowed to speak into the record only if recognized  
19 by the Chair. We look forward to a productive meeting.

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

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

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

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

10 DR. BRIGGS: The Food and Drug  
11 Administration, FDA, is convening today's meeting of  
12 the Endocrinologic and Metabolic Drugs Advisory  
13 Committee under the authority of the Federal Advisory  
14 Committee Act, FACA, of  
15 1972.

16 With the exception of the industry  
17 representative, all members and temporary voting  
18 members of the committee are special government  
19 employees, SGEs, or regular federal employees from  
20 other agencies and are subject to federal conflict of  
21 interest laws and regulations.

22 The following information on the status of

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1 this committee's compliance with federal ethics and  
2 conflict of interest laws, covered by but not limited  
3 to those found at 18 USC, Section 208, is being  
4 provided to participants in today's meeting and to the  
5 public.

6           FDA has determined that members and temporary  
7 voting members of this committee are in compliance with  
8 federal ethics and conflict of interest laws. Under 18  
9 USC, Section 208, Congress has authorized FDA to grant  
10 waivers to special government employees and regular  
11 federal employees who have potential financial  
12 conflicts, when it is determined that the agency's need  
13 for a particular individual's services outweighs his or  
14 her potential financial conflict of interest.

15           Related to the discussions of today's  
16 meeting, members and temporary voting members of this  
17 committee have been screened for potential financial  
18 conflicts of interest of their own, as well as those  
19 imputed to them, including those of their spouses or  
20 minor and children, and for purposes of 18 USC, Section  
21 208, their employers.

22           These interests may include investments,

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

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

12           This is a particular matters meeting during  
13 which specific matters related to Janssen's Invokana,  
14 canagliflozin, will be discussed. Based on the agenda  
15 for today's meeting and all financial interests  
16 reported by the committee and temporary voting members,  
17 no conflict of interest waivers have been issued in  
18 connection with this meeting.

19           To ensure transparency, we encourage all  
20 standing committee members and temporary voting members  
21 to disclose any public statements that they have made  
22 concerning the product at issue.

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1           With respect to FDA's invited industry  
2 representative, we would like to disclose that Dr. Mads  
3 Frederik Rasmussen is participating in this meeting as  
4 a non-voting industry representative, acting on behalf  
5 of regulated industry.

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

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

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

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

22           DR. KNOWLER: Yeah, I would just like to

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

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

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

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

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

1 willingness to participate.

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

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

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

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

1 with declining renal function.

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

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

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

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

1 and moderate renal impairment.

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

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

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

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

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

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

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

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

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

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

5           The question should not be interpreted as  
6 simply asking whether the upper bound of the 95 percent  
7 confidence interval around the hazard ratio derived  
8 from the analysis of cardiovascular safety is below  
9 1.8.

10           For this question, we want you to weigh the  
11 totality of the evidence surrounding cardiovascular  
12 safety, including the issues raised in discussion point  
13 3, and tell us whether you have concerns in concluding  
14 that a cardiovascular risk margin of 1.8 has truly been  
15 excluded for canagliflozin. In your answer, we would  
16 like you to explain why you are or why you are not  
17 concerned.

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

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

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

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

13                       SPONSOR PRESENTATIONS

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

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

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

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

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

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

1 treatment option for patients with type 2 diabetes.

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

8 The proposed dose and administration is 100  
9 or 300 milligrams once daily with specific  
10 recommendations for patients who should start with the  
11 100 milligram dose. These indication and dosing and  
12 administration recommendations or proposals are based  
13 on an extensive Phase III development program.

14 In fact, the largest type 2 diabetes mellitus  
15 program submitted to health authorities to date, with  
16 10,301 subjects enrolled in the Phase III program.  
17 There was long duration of treatment with greater than  
18 2,800 subjects treated with canagliflozin for a year  
19 and a half or more.

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

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

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

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

1 efficacy data.

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

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

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

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

1 have for managing it.

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

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

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

1 behind this increase.

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

8           There are now an estimated 25.8 million  
9 people with diabetes in the United States. That  
10 represents 11.3 percent of the adult population. And  
11 even more frighteningly there are now estimated to be  
12 79 million people with prediabetes, defined as impaired  
13 fasting glucose or impaired glucose tolerance.

14           And the lifetime risk of developing diabetes  
15 for people born in the year 2000, so that's the 12 to  
16 13- year-old children, is now estimated to be 33  
17 percent for men and 39 percent for women. There's a  
18 tremendous economic cost of this epidemic of diabetes.

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

1 billion dollars.

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

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

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

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

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

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

1 set targets for hemoglobin A1c in our population.

2           Currently, the American Diabetes Association  
3 goal is less than seven percent. The American  
4 Association of Clinical Endocrinologists and the  
5 American College of Endocrinology recommend less than  
6 6.5 percent as an appropriate target for A1c, but both  
7 organizations recognize that the closer we can get to  
8 normal value, that is six percent without significant  
9 hypoglycemia or other limiting factors, is really what  
10 our target should be.

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

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

1 improve our glucose levels in this population.

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

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

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

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

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

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

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

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

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

22           So one of the major goals that we have now is

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17                  Canagliflozin pharmacologically lowers the  
18 renal threshold for glucose to a maximal lowering of  
19 the renal threshold for glucose to approximately 70 to  
20 90 milligrams per deciliter. This too is an important  
21 threshold as it is above the threshold typically  
22 associated with hypoglycemia, and thus would mean that

1    canagliflozin would have a low risk for hypoglycemia.

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

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

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

22                   As you heard earlier from Dr. Horton, type 2

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1    canagliflozin 300 milligrams provided consistent  
2    lowering on A1c.

3                    The canagliflozin 100 milligram dose provided  
4    a placebo-subtracted lowering of approximately 0.6 to  
5    0.75 percent. Canagliflozin 300 milligram dose  
6    provided additional A1c lowering and the A1c range  
7    between 0.7 and 0.9 percent. I first call your  
8    attention to the monotherapy study where we saw larger  
9    placebo-subtracted changes.

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

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

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

8           In addition to lowering in A1c, body weight  
9 was also improved. The canagliflozin 100 milligram  
10 dose provided placebo-subtracted approximately a two  
11 percent lowering on body weight. And the canagliflozin  
12 300 milligram dose provided additional body weight  
13 lowering, approximately three percent placebo-  
14 subtracted.

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

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

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

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

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

8           In addition, in a pre-specified step-down  
9 procedure, we also assessed whether or not the doses  
10 would superior to glimepiride. This was done was  
11 assessing the upper bound of the confidence interval  
12 because less than zero. As you can see, canagliflozin  
13 300 milligram dose had an upper bound of the confidence  
14 interval less than zero, and thus statistical  
15 superiority was claimed.

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

22           Relative to glimepiride, canagliflozin 100

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

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

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

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

5               In contrast, canagliflozin 300 milligrams  
6   achieved a relatively stable profile over the remaining  
7   52-week period. At the end of the 52-week period, the  
8   difference between the two treatment arms was that  
9   canagliflozin lowered A1c relative to sitagliptin by  
10   approximately 0.37 percent on A1c. The primary testing  
11   strategy in this study was the same as in the prior  
12   active-controlled study in which we first tested for  
13   non- inferiority with a prespecified margin of 0.3  
14   percent, and then tested for statistical superiority  
15   with an upper bound of zero for the 95 percent  
16   confidence interval.

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

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

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

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

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

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

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

8                    This population of renal impaired patients  
9    also was rather large, consisting of over a thousand  
10   subjects, so provided additional information on this  
11   important population. With a similar baseline mean A1c  
12   of 8.1 percent, we can see that canagliflozin 100 and  
13   300 milligrams lowered A1c from baseline by  
14   approximately 0.5 and 0.6 percent.

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

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

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

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

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

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

1 subjects achieving the important Alc goal of less than  
2 seven percent.

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

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

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

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

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

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

11           Now four of these studies had common design,  
12 common enrolment criteria, differing only by the  
13 background diabetes treatment, enrolled a general type  
14 2 diabetes population, not selected for specific  
15 baseline characteristics. These studies were all  
16 placebo- controlled, 26 weeks in duration and so  
17 provided important pooled dataset. I'll refer to this  
18 as the placebo-controlled studies dataset, and I think  
19 in the FDA briefing book it's also referred to as  
20 Dataset 1 or  
21 DS1.

22           The next dataset we created we referred to as

1 the broad dataset and it's also referred to as Dataset  
2 3 or DS3. This included eight of nine of the Phase III  
3 studies, all of the studies that included both doses of  
4 canagliflozin. This was large dataset including over  
5 9,400 subjects.

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

13 This reflects I think a fairly typical Phase  
14 III diabetes study population and a similar proportion  
15 of males and females mean age in the mid-50s. As you  
16 can see, a duration of diabetes of a bit longer than  
17 seven years reflecting the inclusion of both  
18 monotherapy and add-on to dual therapy studies. About  
19 20 percent of these patients at baseline already had  
20 microvascular complications.

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

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

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

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

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

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

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

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

22           These individually and frequently led to

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

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

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

22           These were generally assessed as mild to

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 risk:

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

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

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

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

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

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

13           Now in this slide I'm showing the hazard  
14 ratios for each of the individual types of events  
15 within the composite. As you can see, on the top  
16 row the composite of 0.91. The hazard ratios for the  
17 individual types of events, CV death, fatal and non-  
18 fatal MI, and unstable angina were less than 1.0, and  
19 the hazard ratio for fatal or non-fatal stroke above  
20 1.0. But as you can see, the 95 percent confidence  
21 intervals around these estimates included 1.0,  
22 indicating that these differences would not be

1 statistically significant.

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

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

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

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

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

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

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

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

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

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

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

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

1 events occurred with relative balance: seven in the  
2 100 milligram group, and six in the 300 milligram  
3 group.

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

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

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

22           Further assessment of this -- I'd like to

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

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

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

1 also note the lack of dose relationship.

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

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

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

1 assessment of this over time is appropriate.

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

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

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

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

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

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

1 attenuation back towards baseline for eGFR.

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

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

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

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

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

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

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

22 Now I'd like to turn briefly to talking about

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

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

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

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

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

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

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

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

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

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

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

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

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

4           We saw only small changes in serum potassium.  
5 Hyperkalemia was infrequent. It was more common on  
6 the background of ACE inhibitors, ARBs, or particularly  
7 when we saw more severe hyperkalemia in patients who  
8 had multiple risk factors; were on potassium-sparing  
9 diuretics, aliskiren, or ACE inhibitors.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 conducted a large Phase III program with more than  
2 10,000 subjects randomized. There was a substantial  
3 proportion, about half of our subjects in the broad  
4 dataset, from more vulnerable populations.

5                   We found that both doses of  
6 canagliflozin were overall well-tolerated with a low  
7 rate of discontinuations related to adverse events.  
8 The incidence of serious adverse events and deaths was  
9 comparable to control. And the safety and tolerability  
10 profile was generally similar across the eGFR range  
11 above  
12 30.

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

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

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

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

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

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

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

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

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

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

1    reduce the risk of these macrovascular complications.

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

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

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

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

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

11           I can speak to this from personal experience,  
12 because I did the same thing. We also see weight gain  
13 with various agents and most of our patients with type  
14 2 diabetes are obese and we wish they would lose  
15 weight, rather than gain weight. Often  
16 gastrointestinal side effects limit use of drugs at  
17 their maximally effective doses.

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

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

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

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

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

1 populations starting with a low dose and working up.

2 Or if a high-dose, if the 300 is used, it permits

3 reduction in that dose.

4               Now, one must balance these benefits against

5 risks that have been identified. You've seen that

6 there's an increase in genital mycotic infections. A

7 small increase in urinary tract infections, but I point

8 out these are lower urinary tract infections and they

9 were not associated with severe adverse events.

10              There was a dose-related higher incidence of

11 reduced plasma volume-related events, a dose-related

12 increase in LDL cholesterol, and a small reduction in

13 bone mineral density. However, I'd like to point out

14 that all of these risks are manageable quite readily in

15 clinical practice.

16              So let me summarize. With the proposal of

17 canagliflozin we would have flexible dosing with 300

18 and 100 milligrams to meet individual needs of

19 patients. I think the data has clearly demonstrated a

20 favorable benefit risk profile, and an agent such as

21 canagliflozin should provide a valuable addition to

22 help meet needs of our patients. Thank you. Clarifying

1 Questions from the Committee

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10 And there's a clustering of these hypotensive  
11 intravascular volume events, is your slide 75, which is  
12 in the briefing document, figure 26 I think, which is  
13 concerning. I mean there's clearly an imbalance at the  
14 300 milligram -- it's a fairly rapid onset event.

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

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

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

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

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

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

1 leading to other complications or problems.

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

7           DR. THOMAS: Dr. Lewis?

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

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

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

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

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

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

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

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

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

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

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

1 the non-CANA group and only minimally different in the  
2 300 milligram group.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16           DR. BRITTAIN: Okay.

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

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1 DR. BRITTAIN: Thank you.

2 DR. THOMAS: Dr. Knowler?

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

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

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

1 based upon individualization.

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

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

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

19                  DR. THOMAS: Dr. Brittain?

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

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

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

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

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

1 safety trial, which is an ongoing trial.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20 DR. THOMAS: Dr. Kaul?

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

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

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

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

22                  However, I will comment that in the original

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

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

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

1 ongoing cardiovascular assessment.

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

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

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

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

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

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

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

1 outcomes of unstable angina or stroke.

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

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

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

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

21 DR. THOMAS: Dr. Cooke?

22 DR. COOKE: Just a simple question. In the

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

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

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

15 DR. THOMAS: Dr. Capuzzi?

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

1 just by obliterating the charge.

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

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

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

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

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

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

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

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

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

12 (A recess was taken.)

13 FDA PRESENTATIONS

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

20 Canagliflozin: Clinical Efficacy and Safety

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

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

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

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

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

22           Lowering this threshold leads to increased

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

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

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

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

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

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

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

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

1 discussed in the previous slide.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22           The figures also suggest that patients with

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

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

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

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

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

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

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

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

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

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

12           In other subgroups shown here in red, such as  
13 use of ACE or ARB at baseline, in particular combined  
14 with diuretics, lower systolic blood pressure, and  
15 longer duration of diabetes, also suggests two to  
16 three-fold increase in the incidence of volume  
17 depletion events with the higher dose of canagliflozin,  
18 300 milligram, compared to non-canagliflozin.

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

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

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

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

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

22           Next we will discuss renal safety. In the

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

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

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

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

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

10           This figure shows the mean change in  
11 estimated GFR over time in patients at a high  
12 cardiovascular risk who are enrolled in the  
13 cardiovascular outcome trial, DIA3008. This trial also  
14 had the longest duration of follow-up, although the  
15 number of subjects drop-off significantly after week  
16 39.

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

1 and the mean baseline GFR was 77 mL per minute.

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

8           Incidences from three datasets are presented  
9 in this slide: DS1, DS2, and DIA3004. Patients in DS1  
10 again had normal to moderate renal impairment. DS2 and  
11 3004 both included patients with baseline renal  
12 impairment, but the overall renal function was slightly  
13 worse in 3004 compared to DS2. The mean GFR was 40 mL  
14 per minute in DS2 and 40 mL per minute in 3004.

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

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

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

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

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

1 by baseline use of ACE inhibitor or ARB agent in study  
2 3004. Figure on the left show the potassium change in  
3 patients who are not on ACE or ARB, and the figure on  
4 the right shows the potassium change in patients who  
5 are on ACE or ARB agents at baseline.

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

12           The figure on the left shows the potassium  
13 change in patients who are not on potassium-sparing  
14 diuretics; the figure on the right shows the changes in  
15 patients who are on potassium-sparing diuretics. There  
16 was a larger increase in the mean serum potassium  
17 levels with canagliflozin in patients who were on  
18 potassium- sparing diuretics. This graph and table  
19 presents the incidence of hyperkalemia-related adverse  
20 events in DS1 and DS2.

21           There is an increased incidence of  
22 hyperkalemia events with canagliflozin in patients

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

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

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

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

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

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

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

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

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

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

12           Paradoxically, there was a slight decrease in  
13 1,25 dihydroxy vitamin D level with canagliflozin. The  
14 mean serum parathyroid hormone decreased with  
15 canagliflozin compared to placebo. And similar to what  
16 to what was observed in DS1, there was a slight  
17 increase in serum calcium and phosphate levels with  
18 canagliflozin.

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

1 there was an early rise in calcium levels which was  
2 dose dependent. There was a wide variation in calcium  
3 changes from study  
4 3004.

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

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

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

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

5           The study included a 26-week core double-  
6 blind period, followed by a 78-week double-blind  
7 extension period, and at the time of NDA submission,  
8 20-week results were submitted. The applicant  
9 submitted 52-week interim data at the end of November.  
10 This table summarizes the placebo-adjusted changes in  
11 bone turnover markers, as well as change in estradiol  
12 and parathyroid hormone levels at 26 and 52 weeks.

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

22           An increase in another bone formation marker,

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

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

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

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

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

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

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

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

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

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

1 appear to occur as early as 12 weeks where the  
2 separation of blinks occur.

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

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

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

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

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

15           To search for female genital mycotic  
16 infections, the safety dataset was searched using the  
17 preferred terms shown in this slide. The incidence of  
18 female genital mycotic infections in DS1, DS2, 3010 and  
19 3008 are presented in this table.

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

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

3           The incidence of female genital mycotic  
4 infections was higher with canagliflozin for all  
5 datasets and was not dose dependent. There was three-  
6 fold higher incidence with canagliflozin compared to  
7 placebo in DS1, and five to seven-fold higher incidence  
8 with canagliflozin compared to placebo in DS2, study  
9 3010, and  
10 3008.

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

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

1 compared to 16 days with placebo.

2           To search for male genital mycotic  
3 infections, the safety dataset was searched using the  
4 preferred terms listed in this slide. The incidence of  
5 male genital mycotic infections in DS1, DS2, 3010, and  
6 3008 are presented in this slide. The incidence of  
7 male genital mycotic infections was higher with  
8 canagliflozin compared to placebo.

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

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

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

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

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

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

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

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

3           This increase in LDL was seen at week 18 and  
4 persisted until the end of study. The LDL levels in  
5 these studies were calculated using Friedwald equation  
6 in these trials, and directly measured LDL in study  
7 3005 and 3006 were consistent with the calculated LDL  
8 levels.

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

13           This graph shows the measurement of Apo B by  
14 treatment group from two studies; 3005 on the left,  
15 3006 on the right. Again, the green is placebo, the  
16 blue is CANA 100, and red is CANA 300. The results  
17 show that there was a dose dependent increase in Apo B  
18 levels, suggesting that LDL level increase with  
19 canagliflozin is due to an increase in particle  
20 numbers.

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

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

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

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

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

1 ratio was 0.91.

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

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

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

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

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

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

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

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

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

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

13                  The timing of these volume depletion events  
14 coincided with reductions in systolic and diastolic  
15 blood pressure, which was observed at the earliest  
16 ascertained time point in Phase III trials.

17 Canagliflozin was associated with a rise in markers of  
18 bone turnover.

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

1    increase in mean serum calcium levels.

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

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

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

19                  Canagliflozin: Statistical Assessment of CV  
20   Safety

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

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

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

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

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

1 glimepiride in one trial, and sitagliptin in another.

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

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

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

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

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

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

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

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

22 As we would hope, due to the randomization we

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

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

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

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

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

3           The comparison in the prespecified analysis  
4 plan was to look at canagliflozin versus all  
5 comparators. So the canagliflozin arm pools both the  
6 100 and the 300 milligram doses, and the all comparator  
7 arm pools both placebo, glimepiride, and sitagliptin  
8 controls. Again to note from previous slide is that  
9 majority of these trials were placebo-controlled. So  
10 there's only one trial with glimepiride and one trial  
11 with sitagliptin.

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

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

1 and adjudicated.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6           When we look beyond 30 days within CANVAS, we  
7 do see results that do favor canagliflozin, with a  
8 point estimate of 0.89 and a confidence interval of  
9 0.64, with an upper bound of 1.25. In the non-CANVAS  
10 set of trials, we do see results that do favor  
11 canagliflozin as shown with an estimated hazard ratio  
12 of 0.64, and confidence interval 0.34 to 1.19.

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

22           And one thing to note here is that there are

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

8                   And what's shown in this slide is a post hoc  
9 sensitivity analysis where we're looking at the first  
10 30 days. What we observed in our data was one event as  
11 shown. However, if you look at the full set of events  
12 throughout the course of treatment in the CANVAS trial  
13 and if we would look at any given 30 day time window,  
14 we have expected to see about 3.76 events, if we assume  
15 there is a constant hazard in the placebo arm.

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

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

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

13           So now I'll summarize our findings. The  
14 first is that the prespecified meta-analysis of the  
15 MACE-plus composite endpoint resulted in a hazard ratio  
16 estimate of 0.91, with a confidence interval of 0.68 to  
17 1.21. This was done by the use of a COX proportional  
18 hazards model.

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

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

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

9           If we look at the set of events that occurred  
10 after day 30 in the CANVAS trial, we have an estimated  
11 hazard ratio of 0.89 with a confidence interval of 0.64  
12 to 1.25. Looking at the first 30 days within CANVAS,  
13 we do have a high estimated hazard ratio, 6.49, with  
14 the 95 confidence interval 0.85, and an upper bound  
15 49.64.

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

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

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

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

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

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

1 make a determination to say that proportional hazards  
2 holds.

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

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

11           DR. SOUKUP: That's correct.

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

14           DR. THOMAS: You want to address that?

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

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

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

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

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

16 DR. THOMAS: Dr. Brittain?

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

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

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

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

20           DR. BRITTAIN: What I'm saying is you're  
21 comparing to -- you're saying once you've survived the  
22 30 days, you're now comparing the -- getting the hazard

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

5 DR. SOUKUP: Right. You are correct in that.  
6 The denominators though -- and I agree, we do lose some  
7 of the randomization because of that, but the  
8 denominators are very similar at that time point after  
9 30 days at the, at least the initiation of day 30, we  
10 do see there are very similar --

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

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

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

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

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

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

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

18 DR. PALEVSKY: Has the sponsor?

19 DR. THOMAS: Dr. Hiatt?

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

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

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

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

11 DR. SOUKUP: Well that, I mean the data we're  
12 looking at is the data that -- I mean it's the  
13 prespecified analysis that was agreed upon. The trial  
14 is still ongoing for CANVAS as you heard this morning,  
15 however, it's been fully recruited, so the early events  
16 -

17 -

18 DR. HIATT: Won't change.

19 DR. SOUKUP: -- won't change.

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

1 with sponsor on how you'd analyze those data?

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

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

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

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

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

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

22 DR. STEIN: Yes.

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1 DR. THOMAS: Dr. Kaul?

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

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

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

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

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

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

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

22           DR. SOUKUP: No, I think that very clearly

1 covers the issues.

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

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

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

1 be a precedent setting example.

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

9           DR. PARKS: I actually have a question for  
10 you first and then I'll try to answer your question.  
11 You said that you had concerns about unblinding the  
12 ongoing trial. Is your concern here for the 1.8 or  
13 1.3, because again we're talking about two different  
14 risk margins? And then with respect to regulatory  
15 precedent and looking at one trial or interim analysis  
16 of an ongoing trial, from our standpoint things have  
17 come in, whether -- and we have considered this, but  
18 nothing in the public domain that can be presented.

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

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

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

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

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

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

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

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

13 DR. THOMAS: Dr. Proschan?

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

22 One way of putting that all together is to

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

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

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

19 DR. PROSCHAN: The other question was whether  
20 --

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

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

3 DR. THOMAS: Any other questions, Dr.

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

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

22 For this reason, FDA encourages you, the open

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

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

15           The FDA and this committee place great  
16 importance in the open public hearing process. The  
17 insights and comments provided can help the agency and  
18 this committee in their considerations of the issues  
19 before them.

20           That said, in many instances and for many  
21 topics, there will be a variety of opinions. One of  
22 our goals today is for this open public hearing to be

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

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

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

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

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

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

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

9               Given all of the costs associated with  
10  diabetes, we can't keep going with this current status  
11  quo environment. The most costly one percent of people  
12  with diabetes incur expenses of \$100,000 a year,  
13  according to a 2009 study in pharmacoeconomics. And  
14  the most costly one-tenth of one percent have expenses  
15  of nearly \$1 million a year. So 200 patients costing  
16  \$100,000 a year is \$20 billion. Twenty-thousand  
17  patients costing \$1 million a year is another \$20  
18  billion.

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

1 outcomes associated with diabetes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7           We heard about it's the leading cause of  
8 blindness in adults, kidney failure, lower limb  
9 amputations, and we heard about the other horrible  
10 complications and morbidity and mortality of patients  
11 with diabetes. We also heard that the control of type  
12 2 diabetes remains suboptimal, even though we have  
13 tools available to us.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 hypoglycemia and weight gain. Thank you very much.

2 DR. THOMAS: Thank you for your comments.

3 We'll move to open public hearing speaker number three  
4 please.

5 PAULINA DUKER: Good afternoon. I'm Paulina  
6 Duker, an advanced practice nurse and a certified  
7 diabetes educator, serving as the Vice President of  
8 Diabetes Education and Clinical Programs at the  
9 American Diabetes Association. The ADA represents  
10 15,000 professional members, and nearly 26 million  
11 Americans with diabetes. I have no conflicts,  
12 financial or otherwise.

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

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

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

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

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

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

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

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

1 hypoglycemia.

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

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

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

22           Obesity is a national epidemic, with the CDC,

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

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

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

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

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

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

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

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

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

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

8           On the other hand, when you look at the data  
9 on canagliflozin, in just 30 days, again this same  
10 first 30 days where a number of other problems have  
11 arisen, there was one event in the placebo group, for  
12 0.3 percent, and 16 in the canagliflozin group for 2.3,  
13 and that obviously was highly statistically  
14 significant.

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

22           Part of volume depletion can include

1 hemoconcentration. And what I did here is take the  
2 data from dapagliflozin and compare it to the data we  
3 now have on canagliflozin. And this is the absolute  
4 increase in hematocrit, so 1.57 would be from 45 to  
5 46.7 (indiscernible). And what you can see is that  
6 there is much more of an increase in hematocrit in the  
7 people getting canagliflozin, 1.5 times as much as the  
8 dapa group in both doses. It's a little bit lower in  
9 the high dose.

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

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

1 polycythemia vera or any other source of polycythemia.

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

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

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

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

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

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

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

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

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

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

11 BENNETT DUNLAP: Good afternoon. Thank you  
12 for this opportunity to comment on diabetes  
13 medications. My name is Bennett Dunlap. I'm an  
14 ePatient advocate and write the blog Your Diabetes May  
15 Vary. I have a Master's degree in health  
16 communications that certainly didn't prepare me to  
17 pronounce things like canagliflozin. I have no  
18 relationship with the sponsor.

19 A portion of my gas and tolls today is being  
20 paid by the Diabetes Advocates, an association of  
21 patients and social media writers. We see social media  
22 as an important way for patients to become informed

1 about options to consider with their healthcare  
2 professionals.

3           Four years ago my primary care physician told  
4 me I had elevated fasting glucose levels. As Kelly  
5 mentioned, there's not enough endocrinologists and  
6 specialists, and it took me a half a year to get an  
7 appointment to confirm that I was in fact type 2, which  
8 wasn't a really big surprise because I have a father  
9 and sister who are type 2, and two of my kids are type  
10 1.

11           My father and sister have been the  
12 beneficiaries, and I have been the beneficiary, of  
13 different care plans for our respective type 2  
14 diabetes, each tailored to our individual situations.  
15 And I'm confident that just as my family care varies,  
16 so do the needs of other individuals in the population  
17 of diabetes patients in the United States. So I'm  
18 pleased to see that the drug under consideration today  
19 was studied with a wide range of individuals. Like  
20 other options, it may be a better choice for some  
21 patients than others.

22           I love Kelly's comments, when she said that

1 we need type 2 drug options that people take, and that  
2 work. Each of us deserves the opportunity to work with  
3 our healthcare professionals to find the mix of  
4 medications, that in combination with lifestyle  
5 changes, successfully helps us manage blood sugar  
6 levels. Many of us may benefit from, even if we cannot  
7 pronounce, canagliflozin. And I got closer that time.

8               This class of medication offers an exciting  
9 opportunity for a new means of glucose control.  
10 Significantly, as has been said, there's a reported  
11 mix, or a reported lower level of hypoglycemia. Dr.  
12 Grunberger and Ms. Duker made it very clear that  
13 hypoglycemia matters. Fear of hypos is a deterrent to  
14 compliance, even for those of us that should know  
15 better. I found it significant this morning to hear  
16 that one of the medical professionals involved with the  
17 studies had that experience themselves.

18               SLG2 (sic) therapies may offer something  
19 beyond medication to improve glucose levels without  
20 increasing the fear of lows. They may offer health  
21 practitioners a small piece of art that may be akin to  
22 magic for some of us patients.

1           Type 2 diabetes is invisible. I certainly  
2 had no symptoms, but my blood sugars were spinning out  
3 of control. Also, progress towards successfully  
4 managing diabetes is just as difficult to perceive. I  
5 often feel that medical literature, with possibly the  
6 exception of my friend from AACE -- did I get it right  
7 -- projected diabetes care as easy and that results are  
8 the straightforward implications of switching on  
9 something called compliance.

10           I know that I and other patients have felt  
11 frustration when we have found the process to be very  
12 difficult. Even more so, when the lack of expected  
13 results is seen by providers as a failure of compliance  
14 and effort on our part when some of the treatments we  
15 have been given have known side effects to thwart those  
16 very expectations.

17           For some the next few pounds are harder to  
18 lose than previous 30. The next half point of A1c is  
19 harder to achieve than the first, despite taking good  
20 care and doing what we've been prescribed.

21           The lack of symptoms in type 2 diabetes makes  
22 it easy for patients like myself to spin out of

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1 control. Diabetes self-care is not easy, particularly  
2 when what patients see from treatments is weight gain  
3 and frightening lows.

4           This medication may be a tool physicians can  
5 use to help stop some patients from spinning out of  
6 control. It may help us see emotionally tangible  
7 results that, without hypos, that promote healthy  
8 lives. And for those healthier lives, I thank you all.

9           DR. THOMAS: Thank you for your comments.  
10 And I also too have trouble with many of the names that  
11 come before this committee as well, so you're not  
12 alone.

13           The open public hearing portion of this  
14 meeting has now concluded and we'll no longer take  
15 comments from the audience. Questions to the  
16 Committee/Committee Discussions

17           DR. THOMAS: The committee will now turn its  
18 attention to address the task at hand, the careful  
19 consideration of the data before the committee, as well  
20 as the public comments.

21           We do have a list of names from this morning  
22 that did not get a chance to ask questions, so we'll

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1 use that. And also, if you have a question that you'd  
2 like to ask, please raise your hands and we can add you  
3 to the list.

4 But before we get started, Dr. Brittain had  
5 asked the sponsor if they were able to provide some  
6 additional data and I was wondering if you were able to  
7 obtain that or not. Yeah, I think that was correct,  
8 right? If you have it, if not, that's fine. Okay,  
9 well just give us a signal when you have that. Dr.  
10 Gregg?

11 DR. GREGG: Sure. So these are remnants from  
12 this morning, but I actually had two separate  
13 questions. The first is that given the large blood  
14 pressure reductions that were seen, apparently through  
15 a different mechanism than ordinary, I'm wondering  
16 whether, in these trials, whether there's any attempt  
17 to examine how the profile of concomitant treatments  
18 changed over time, over that two years.

19 Specifically whether there's compensation in  
20 terms of the prescription of other drugs, potentially  
21 protective, that happened in response to those blood  
22 pressures. So more specifically, I'm wondering whether

1 the medication changed over time.

2           The second question is really unrelated to  
3 that, but it has to do with the characteristics of the  
4 populations in all these studies, which on the whole  
5 appear relatively representative. But the sort of  
6 glowing exception of that is that there's only two or  
7 three percent, maybe four percent African-Americans in  
8 these studies.

9           And this is, you know nationally, this is 15  
10 or 20 percent of the population, really even more if we  
11 were to think about the target population for this  
12 drug. And I'm curious as to whether in the meta-  
13 analysis, or the pooled analysis, you're able to look  
14 at that subgroup.

15           DR. STEIN: With regard to changes in  
16 medication over time, I think perhaps one medication  
17 which might be considered as a likely change would be  
18 ACE and ARB therapy since it's the most common anti-  
19 hypertensive therapy.

20           If I could have the slide up, slide up. So  
21 what we looked at here are subjects who had ACE or ARB  
22 therapy at baseline. This is from our broad dataset,

1 so this is over about 16 months of average duration of  
2 exposure.

3           And I think you can see that, first of all,  
4 that about two-thirds of our subjects were on an ACE or  
5 ARB at baseline. And then the change in that was  
6 relatively minimal. There was a small reduction in the  
7 use of ACE or ARB therapy that was not particularly  
8 different across the treatment groups.

9           On the other hand, if you look at diuretics,  
10 slide up, a similar type of observation. Again, the  
11 top row looks at the proportion of individuals, again  
12 from our broad dataset, who were on diuretics at  
13 baseline.

14           And you can see perhaps a slight reduction  
15 with canagliflozin, but a reduction also in the non-  
16 canagliflozin group. So I think the conclusion we came  
17 to was there wasn't a dramatic modification of the  
18 concomitant medication regimens.

19           You asked about the information in the  
20 African- American population. We have looked both at  
21 the pharmacokinetic, pharmacodynamic efficacy and  
22 safety responses and I can comment through those, just

1 briefly, if I may.

2           So with regard to the pharmacokinetic  
3 exposure, it doesn't appear to be any meaningfully  
4 different by ethnic groups, and in particular not  
5 different in individuals who are African-American.

6           In regards to the pharmacodynamics response,  
7 I'll say that we have relatively limited information in  
8 the small numbers that we have pharmacodynamics  
9 information, and here I'm referring to the endpoint  
10 which we were using, which was the renal threshold for  
11 glucose.

12           Canagliflozin lowers that threshold and we  
13 looked at that in individuals with different ethnic and  
14 racial backgrounds and really didn't notice very much  
15 differences at all, which I think we anticipate since  
16 the expected effect of the level of kidney would likely  
17 be similar.

18           We've also looked at efficacy across  
19 different ethnic groups. And maybe I'll ask Dr.  
20 Meininger just to comment just very briefly on the  
21 efficacy, and then we can also show you some safety  
22 data in African-American subjects.

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1                   GARY MEININGER: Right. So just to remind  
2 you, across the Phase III program, we enrolled  
3 approximately 450 subjects. Again, the majority of  
4 black or African- American subjects came from the  
5 United States, and of the proportion that we recruited,  
6 represented about 14 percent, so consistent with the  
7 proportion that you were quoting in terms of the United  
8 States.

9                   Slide up. In terms of efficacy, I showed  
10 this slide earlier in terms of the subgroup analysis.  
11 And if you turn your attention to the third grouping of  
12 race, you can see that there was no interaction of race  
13 with being white, black or African-American, Asian or  
14 other, both for the canagliflozin 100 milligram dose as  
15 well as for the canagliflozin 300 milligram dose.

16                  DR. STEIN: Thanks, Gary. Slide up, and then  
17 just very briefly with regard to safety. This is the  
18 experience, again, in our broad dataset, and you can  
19 see that we had a moderate number of individuals in  
20 this dataset that were black or African-American.

21                  As you can see, the overall incidence of  
22 adverse events, not notably different, slightly higher

1 at 100, not notably different at 300; adverse events  
2 leading to discontinuation, serious adverse events, and  
3 deaths not notably different; adverse events related to  
4 study drug modestly increased, as we've seen across our  
5 program. Those are largely the genital mycotic  
6 infections and the polyuria, polydipsia, thirst that  
7 account for those differences.

8           And so this profile is quite similar to what  
9 we've seen across the broad dataset. So our conclusion  
10 was that PK pharmacodynamic response, the efficacy  
11 response, and the safety profile don't appear to be  
12 meaningfully different.

13           DR. THOMAS: Thank you. Ms. Killion? Dr.  
14 Guettier?

15           DR. GUETTIER: I think the sponsor also  
16 provided data on the discontinuation rate for patients  
17 who were on metformin at baseline and maybe that is  
18 something that would be useful to see.

19           DR. STEIN: On metformin at baseline?

20           DR. THOMAS: Is that by racial group or just  
21 --

22           DR. GUETTIER: I recall seeing, in the NDA, a

1 figure which showed the rate of discontinuation of  
2 metformin patients with moderate renal impairment, I  
3 believe.

4 DR. STEIN: I mean in our studies of moderate  
5 renal impairment, we excluded the use of metformin  
6 since it's not indicated in that. So I'm not exactly  
7 sure which slide you're referring to. We do have a  
8 discontinuation rate across the whole program which I  
9 can show. Is that what you're looking for?

10 DR. GUETTIER: We were looking for  
11 discontinuation rate specifically for anti-diabetics,  
12 in  
13 DS1.

14 DR. STEIN: We'll see if we can find that.  
15 I'm not exactly sure.

16 DR. THOMAS: Okay. Maybe when you -- let me  
17 know when you have that.

18 DR. STEIN: Yeah. And if you can provide the  
19 reference to the specific table, I'm sure we'll have a  
20 slide of it. But I'm not exactly sure what you're  
21 referring to.

22 DR. THOMAS: Ms. Killion?

1                   MS. KILLION: I have a question that relates  
2 to the incidence of genital mycotic infections and UTI.  
3 One of my concerns, as you're heard expressed in the  
4 open public hearing, is barriers to adherence. So I'm  
5 a little bit concerned about this and I'd like a little  
6 bit of information clarifying from the sponsor.

7                   Can you clarify for me if the incidences of  
8 these kind of infections were seen more at the  
9 initiation of treatment and dissipated over time? Or  
10 whether there was something that was likely to recur  
11 while you were on this therapy?

12                  DR. STEIN: If I could have the slide up.  
13 And what I'll start with is female genital mycotic  
14 infections, and if you like I'd be happy to provide  
15 similar information with regard to the male genital  
16 mycotic infections.

17                  So this is the Kaplan-Meier for time to event  
18 for the female genital mycotic infections. And as you  
19 can see, in terms of at least the accrual of patients  
20 with first events, what we've seen is that the curve  
21 begins to flatten at around 26 weeks, and then after 52  
22 weeks it's further flattening, so the accrual of

1 additional events appears to be decreasing.

2           With I think the caveat here that the numbers  
3 of subjects, as you go beyond 52 weeks, begins to  
4 decrease. And so the estimates around this I think have  
5 to be taken into -- the confidence around these  
6 estimates would have to be taken into account.

7           If I could, I'll show this similar picture  
8 for the male genital mycotic infections, slide up. So  
9 the pattern here, we saw some slight differences by  
10 dose. But as you can see, here there's a little bit  
11 more of an increase through 52 weeks, but again with  
12 what appears to be a plateau, and once again with the  
13 caveat that the numbers after week 52 are a little bit  
14 more limited.

15           And you asked about recurrence rate, and we  
16 can show you some information that we have about  
17 recurrence rate as well. If I could 564 please.  
18 Thanks. So I'll start with the recurrence rate that we  
19 saw in males, slide up. So this is individuals -- and  
20 again this is in our broad dataset, and just to again  
21 orient you, this is about a 16-month average duration  
22 of exposure, and about three-quarters or more of the

1 subjects who've had at least a year of exposure.

2           The incidence in that dataset, I think I  
3 presented this data earlier, in the top row, as you can  
4 see, the increased incidence with canagliflozin, both  
5 doses, and then looking at the numbers of subjects who  
6 have more than one event in the second row.

7           So overall in the population, about 1.6  
8 percent at canagliflozin 100, 2.7 percent, or 2.1  
9 percent overall with more than one event of a genital  
10 mycotic infection.

11           And then slide up, so this is the same  
12 information for female genital mycotic infections. And  
13 again, the top row is data that I had previously showed  
14 with regard to the incidence of these in this broad  
15 dataset. And then you can see that overall about 4.6  
16 percent of women had more than one of these adverse  
17 events.

18           DR. THOMAS: Dr. Nakela Cook?

19           DR. COOK: Thank you. I actually would like  
20 to ask the sponsor a little bit more about the hazard  
21 ratio for stroke in the studies here. I guess my  
22 concern is that it's hard for me to draw a conclusion

1 as to why we may be seeing this increased hazard ratio  
2 that's in the non-significant range.

3           And I know that we went through several  
4 reasons that the sponsor kind of investigated. But I  
5 guess I wonder if the look at this data being interim  
6 may not just provide us with enough events in order to  
7 really understand whether or not this may represent  
8 true harm. And I wondered if you could speak a little  
9 bit to that, as well as what you think the potential  
10 mechanism would be if this is truly related to harm.

11           DR. STEIN: Well as I commented earlier, I  
12 think our primary assessment is that the composite  
13 endpoint would be the most robust because of the number  
14 of events. And I think in that composite we had a  
15 reasonably sizeable number of events, 200 events. And  
16 the number of events within each of the elements of the  
17 composite being smaller, we expected to see more  
18 variability. Three of the hazard ratios, as I noted,  
19 were below one, and one was above one, the hazard ratio  
20 for stroke.

21           I will note that we did look to see whether  
22 there was any evidence of an exaggerated diuretic

1 response, greater hemoconcentration in individuals with  
2 stroke compared to those who did not have a stroke. We  
3 didn't notice any meaningful differences. We also  
4 looked to see whether there was a greater reduction in  
5 blood pressure, didn't notice any differences in blood  
6 pressure as well.

7           We looked to see whether there was an overlap  
8 with these events that we've been discussing of reduced  
9 intravascular volume-related adverse events that might  
10 reflect dehydration, and we didn't see any meaningful  
11 overlap. There were three individuals who, out of the  
12 47, who had a stroke, who had one of these adverse  
13 events.

14           I commented that the time courses also  
15 appeared to be different, and maybe if we could show  
16 the Kaplan- Meier for -- thank you, slide up -- for  
17 stroke. This, as you can see, appears to particularly  
18 separate at about week 18. And I won't show this  
19 again, but I did comment previously that when you look  
20 at the time to event Kaplan-Meier curves for the  
21 reduced intravascular volume- related adverse events,  
22 those rise, again as we discussed, rather early on,

1 with a peak at around 18, and certainly by 26 weeks  
2 there doesn't appear to be accrual of additional  
3 events. So the Kaplan-Meiers appear to be quite  
4 separate.

5 I commented that the dose dependency was very  
6 evident for the reduced intravascular volume of the  
7 adverse events, but strokes were actually quite the  
8 same in both the 100 and the 300 milligram group.

9 Finally, I think the other point that is  
10 worth making is that if one was to expect to see  
11 dehydration, volume depletion, leading to events that  
12 reflected the hypercoagulable state that that would  
13 induce, one would expect to see that to be generalized.

14 You'd expect to see an increase in venous  
15 thromboembolic phenomenon, which we have not seen any  
16 notable imbalance. And we would have expected to see  
17 this in other arterial beds.

18 And as I commented before, myocardial  
19 infarction and the unstable angina are both events  
20 reflecting a thrombotic diatheses. Both had hazard  
21 ratios less than one. So I think our assessment of  
22 this is that it most likely reflects the play of

1 chance, as again this difference is not a statistically  
2 significant difference.

3 DR. THOMAS: Dr. Kaul, you wanted to follow  
4 up and then we can --

5 DR. KAUL: Yeah. Have you done the breakdown  
6 on the type of stroke, the ischemic versus the  
7 hemorrhagic or undefined? Because we saw the data  
8 presented by the FDA, 37 versus nine ischemic stroke.  
9 They did not show the hazard ratio. Did you do the  
10 analysis to see whether it was significant or not?

11 DR. STEIN: I don't know if we have the  
12 hazard ratio for specifically ischemic strokes. Slide  
13 up. I can again show the distribution of strokes that  
14 we saw, ischemic, hemorrhagic, undetermined. As you  
15 can see, the top table shows across the entire CV meta-  
16 analysis population.

17 The bottom is the CANVAS study information to  
18 show you the types of strokes. It was, as typical, a  
19 predominant of ischemic strokes, but again some  
20 hemorrhagic and undetermined types of strokes as well.

21 DR. KAUL: I mean it stands out in the CANVAS  
22 trial, in the non-CANVAS dataset, and even in the

1 extended phase of the data through November 2012 when  
2 you have 271 events, and I'm kind of curious about  
3 this.

4           This is a lingering concern and whether it's  
5 statistically significant or not is not that big of an  
6 issue, but if you look at the 37 versus nine, I just  
7 did a rough back of the envelope analysis and it  
8 excludes a hazard ratio of one. So for whatever that  
9 is worth.

10           DR. STEIN: Well as you commented, and as was  
11 provided in the briefing book, there was another  
12 analysis done, as requested by the European Medicine  
13 Agency. They asked us to update the information on  
14 stroke. We provided the update in the briefing book.

15           The information's only recently been  
16 submitted to the FDA, so I won't go into any details.  
17 But just to say, slide up, that, as you point out, the  
18 updated analysis showed that with now another  
19 approximately 80 overall MACE plus events, and I think  
20 this is an additional 20 strokes, the hazard ratio, the  
21 original is shown here, 1.47, now the hazard ratio of  
22 1.29. So I think that's consistent, from our

1 assessment, that the initial hazard ratio of 1.47 well  
2 could still reflect the play of chance.

3           One other point I think probably worth making  
4 is that, as I commented before, I think you'd expect if  
5 you were going to see an increase in ischemic strokes,  
6 you would also see an imbalance in transient ischemic  
7 attacks. And as I noted before, the hazard ratio for  
8 the transient ischemic attacks, slide up, and again the  
9 number of events are not large, but the hazard ratio  
10 for transient ischemic attacks shows complete balance.

11           And I think in most studies where there has  
12 been imbalances in strokes, and in studies where  
13 there's been increases, it tends to parallel with more  
14 transient ischemic attacks. In fact often,  
15 particularly in situations of hypercoagulability, one  
16 also sees increased venous thromboembolic phenomenon.  
17 All we've seen is the one event of stroke being  
18 increased, again in non- statistically significant  
19 fashion, with these other types of events not  
20 increased.

21           DR. KAUL: Two quick follow-up. Have you  
22 done an analysis where you've combined TIA with stroke,

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1 number one? And number two, I asked you earlier in the  
2 morning, do we have any idea about what was the impact  
3 of these strokes on patients? In other words, were  
4 they disabling or not?

5 DR. THOMAS: And before you answer, can I ask  
6 the sponsor to be more succinct just because of time  
7 issues? Thank you.

8 DR. STEIN: Certainly. We don't have follow-  
9 up -- we don't have an assessment by disability. We  
10 have not done a pooled analysis with TIAs and stroke.

11 DR. THOMAS: Dr. Hiatt, you had a follow up  
12 on that?

13 DR. HIATT: I don't want to add too much to  
14 this, but it is notable that of the early MACE events  
15 on drug, five of 12 were strokes. The other thing that  
16 I find notable is that most cardiovascular trials, a  
17 composite of MI, stroke or death is dominated by fatal  
18 and non-fatal myocardial infarction. And so the number  
19 of strokes, for whatever reason, seem to be  
20 inordinately high in this cardiovascular outcome trial.  
21 Yeah.

22 DR. THOMAS: Dr. Malarkey?

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1 DR. STEIN: I might just comment that when we  
2 look at other cardiovascular outcome trials, looking at  
3 the incidence of stroke, the incidence we see doesn't  
4 appear to be notably different. I perhaps can show  
5 some data across the literature. Again, I'm not  
6 showing this to --

7 DR. THOMAS: I think we're going to go into  
8 the next question. Dr. Malarkey?

9 DR. STEIN: Okay. Sure.

10 DR. MALARKEY: Thank you. My comments and  
11 questions are in regard to the two-year animal studies.  
12 This was presented in the FDA briefing. There's an  
13 interesting assortment of neoplasms, clearly increase  
14 in incidents, and that includes renal tubular adenomas  
15 and carcinomas, pheochromocytoma, and Leydig cell tumor  
16 of the testis. And there appears to be class effects  
17 in other similar chemical, similar drugs. You see it  
18 in the mice and rats as well.

19 So I'm wondering about the target for this  
20 drug, is the kidney, and it's the site of these lesions  
21 as well. And a kidney lesion might be related to a  
22 pheochromocytoma. So my question is, was there

1   exacerbation of a nephropathy in the kidney that might  
2   have been related to the kidney tumors or the  
3   pheochromocytoma? And was elevated LH found in this  
4   study for the Leydig cell tumors?

5               DR. STEIN: So I'll just make a very quick  
6   comment and then I'm going to actually as Dr. Cohen,  
7   who has helped us with a number of the investigations  
8   that we performed, to summarize some of the  
9   information.

10              Just as a quick lead in, what I comment to  
11   say is that we've done an extensive mechanistic  
12   toxicology program, which I think has demonstrated that  
13   the findings relate to carbohydrate malabsorption that  
14   we see in rats that we don't see in humans.

15              In answer to your question about LH, yes LH  
16   was increased in rats and we've looked at that in our  
17   clinical studies from archive specimens, and  
18   canagliflozin does not increase LH in the clinical  
19   setting. Dr. Cohen?

20              SAMUEL COHEN: Sam Cohen, University of  
21   Nebraska Medical Center. Dr. Stein has adequately I  
22   think addressed the Leydig cell tumor. The renal cell

1 tumor, just to begin with, there was no impact on the  
2 nephropathy that would explain the renal tumors. If I  
3 could have a slide up please? CANA is a selective  
4 SGLT2 inhibitor, but it does have some SGLT1 activity  
5 when it is high enough concentration in the GI tract.

6           And this leads to some inhibition of the  
7 transport of glucose, leading to a malabsorption with  
8 its sequelae of increased pH in the GI tract --  
9 decreased pH in the GI tract and increased calcium  
10 absorption, urinary excretion of calcium.

11           This is also associated with tubular injury  
12 in the kidney that is indicated by Kim-1 and by  
13 histopathology. And there is an increase in cell  
14 proliferation as evident by BrdU labeling. The key is  
15 that this can be -- these effects can all be inhibited  
16 when you inhibit this malabsorption by giving a  
17 fructose- based diet instead of essentially a glucose  
18 and lactose- free diet.

19           This is similar to what had been previously  
20 reported 15, 20 years ago with the carbos, which is a  
21 glucosidase inhibitor and has the same effects on the  
22 carbohydrate malabsorption, with the same associated

1 effects, not only kidney tumors but in  
2 pheochromocytomas.

3           And then in the humans, there's no evidence  
4 that you're getting this malabsorption effect so that I  
5 think that there would be no implications with regard  
6 to human relevance of any of these tumors. Similarly,  
7 with the adrenal tumors, the increase in proliferation  
8 occurs when you're on CANA on a regular diet, and as  
9 soon as you substitute the fructose, that goes away.

10           DR. MALARKEY: Can I follow up? I appreciate  
11 the excellent mechanistic studies that were performed  
12 and agree that it's different in humans than the  
13 rodents. One follow-up question was do they have  
14 pituitary tumors?

15           SAMUEL COHEN: As far as I know, there were  
16 no increase or decrease in pituitary tumors.

17           DR. MALARKEY: Okay. Thank you.

18           DR. THOMAS: Dr. Proschan?

19           DR. PROSCHAN: Yeah, I think one of the  
20 problems I think, with just looking at these raw  
21 numbers like you see 13 to 1, you know 13 in the drug  
22 group and 1 in the placebo group, is, you know we're

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1 not taking into account in our minds the fact that this  
2 is 2 to 1. And so you don't expect 7 to 7, you expect  
3 something more like 9 to 5, or 10 to 4. So 13 to 1  
4 sounds dramatic, but not when you think -- you know,  
5 it's not as dramatic when you think about the fact that  
6 it's a 2 to 1 randomization.

7           The same comment with the 37 and 9. You  
8 know, that's 46 events. You don't expect 23 of them to  
9 be in each arm. You expect something like a 30 to 15  
10 split, or a 31 to 14 split, 30 to 16 or 31 to 15 split.  
11 So I think we have to keep that in mind.

12           The other thing -- and I'm actually, I'm  
13 making comments, I don't have questions, and is this  
14 the wrong time or are we in the comment phase?

15           DR. THOMAS: (Off mic).

16           DR. PROSCHAN: Okay. I'll stop then if we're  
17 not --

18           DR. THOMAS: (Off mic).

19           DR. PROSCHAN: Okay. Well so -- well I'll  
20 wait and say the rest, what I was going to say in the  
21 comment phase.

22           DR. THOMAS: Dr. Lewis?

1           DR. LEWIS: Thank you. Well I'll actually  
2 comment that I'm actually kind of okay with the MACE-  
3 plus thing you've got there. But what concerns me is,  
4 as near as I could discern from the briefing documents,  
5 the physicians in these trials had the ability to  
6 manipulate the patient statins and other cholesterol  
7 lowering agents at will. And despite that, there is  
8 this discrepancy in LDL cholesterol.

9           And I am concerned about whether there has  
10 been sufficient follow-up time of any of the patients  
11 in this trial for us to understand the clinical  
12 consequences of that, because it's probably going to  
13 persist in the real world. Like maybe forever in these  
14 patients because you know the doctors could have fixed  
15 during the trial and they didn't, even though they were  
16 on statins and they could start statins.

17           And if you could -- and I have a second  
18 thing, so I'll say both if it's okay with you. So if  
19 you could comment whether you think that this is  
20 sufficient follow up to see the consequences, a  
21 prolonged increase in LDL cholesterol.

22           And the other thing is hyperphosphatemia has

1   been associated with increased cardiovascular  
2   mortality, not only in renal patients now, but in the  
3   normal population as well, and even within the normal  
4   range. And I wondered if you did any analyses of  
5   whether hyperphosphatemia was a risk factor for  
6   cardiovascular outcomes in this trial, since it's a  
7   consequence of your drug as well.

8                   And I will -- just one other electrolyte  
9   comment. It does lower uric acid, which you know you  
10   don't even list on your maybe good things. However, it  
11   is also uricosuric. And I do think whatever happens,  
12   that does need to be -- doctors need to be reminded of  
13   that. This is a population that eats a lot of purine  
14   and could get in trouble with uricosuria here, but  
15   should also know that it lowers uric acid.

16                  DR. STEIN: Thank you. With regard to the  
17   statin dose changes, the analysis that we've done  
18   particularly looked at the statin dose changes through  
19   the first six months because we wanted to make sure  
20   that that didn't confound the LDL data that we were  
21   presenting.

22                  And I think, as the FDA presentation

1 indicated, there was very little change that occurred.  
2 It was slightly greater over time. But I think the  
3 comment I'd make is that the mean change is a  
4 relatively small one. Not in terms of the discussion  
5 around whether that's meaningful or not, and certainly  
6 we'll have more of, but in terms of the quantitative  
7 change, and given the variability in LDL, I think it  
8 may be hard in individual measurement to see these  
9 kinds of changes. So we didn't see net changes in  
10 statin.

11           The numbers of patients that were increased  
12 or decreased in dose when initiated statin was  
13 relatively modest even over the 18 months of the follow  
14 up in the broad dataset. And as I said, I think that's  
15 just reflects that these were relatively modest  
16 changes.

17           I will say that we asked that the physicians  
18 do their best, prior to run into implement statin  
19 therapy and then to keep them stable if possible, but  
20 they were not proscribed from modifying. And in the  
21 CANVAS trial, we asked that they be aggressive about  
22 it.

1           With regard to the time course, as I showed,  
2 because of the updated analysis that we were requested  
3 to do by the European agency, that was after about 20  
4 months or so, and the hazard ratio wasn't changed. I  
5 certainly would wonder whether the one-year time point  
6 might be sufficient to see the impact of LDL.

7           But I think now that we're going further and  
8 we're not seeing any further change in the hazard  
9 ratio, I think that is likely a sufficient exposure.  
10 Certainly in the statin trials we begin to see  
11 separations, some trials one, two years, in that  
12 timeframe. So I think if we were to see a negative  
13 impact, one might expect that might begin to be seen.

14

15

16           With regard to phosphate, no we have not done  
17 analysis looking at changes in phosphate relative to  
18 outcome, although again, the changes were in the five,  
19 eight percent range. They were relatively small. And  
20 the only other comment I'd make with regard to the  
21 uricosuric comment, we haven't flagged that  
22 extensively, but I do want to say that we did look at

1 renal stones and there was no increase in renal stones.  
2 And we have a very large program, we had a fair number  
3 of stones, but there was no increase, actually slightly  
4 fewer.

5 DR. THOMAS: Dr. Palevsky?

6 DR. PALEVSKY: So I'd like to explore a  
7 couple things about electrolyte disturbances. You had  
8 provided that on the incidence of hyperkalemia, and I  
9 think in the FDA presentation it indicated that the  
10 potassium went up in patients on RAS blockade or  
11 potassium-sparing diuretics, but went down in patients  
12 not on those agents.

13 One would expect, with an osmotic diuresis  
14 that there would be potassium wasting and I didn't see  
15 any data on the incidence of hypokalemia. I'd also  
16 like to know the actual rates of clinically significant  
17 hyperkalemia. If a patient goes up from 4.4 to 4.6,  
18 I'm not all that concerned about it, but if their  
19 potassiums are going up into the upper 5.0s I am. So  
20 if you could present data on percent, on the incidence  
21 of potassiums greater than 5.5.

22 I also didn't see any data on changes in

1 serum sodium concentration. One would expect a risk of  
2 hypernatremia with an osmotic diuretic. So if you  
3 could provide that information.

4 DR. STEIN: Sure.

5 DR. PALEVSKY: Also I did not see, and maybe  
6 I missed it, the data on maximal increase in hemoglobin  
7 concentration. If you could, provide the data on the  
8 peak hemoglobins or peak hematocrits that have occurred  
9 because that would be informative regarding the extent  
10 of the intravascular volume depletion.

11 And finally, there was still some question in  
12 my mind as to how much of the change in kidney function  
13 is purely hemodynamic versus whether there's any  
14 development of structural kidney disease. You  
15 presented some data in the briefing document on NAG.

16 Do you have any data on any of the other  
17 markers of tubular damage that could have been looked  
18 at, Kim-1, which is validated, NGAL, which I don't  
19 think the FDA has accepted as a validated marker, or  
20 any of the other potential markers of tubular injury?

21 DR. STEIN: So if I can start with the  
22 question about potassium. If we could see 2260,

1 SA2260. We'll try to pull it out. It's the histogram  
2 for the potassium distribution changes. Okay, thank  
3 you. So slide up.

4           This is looking at the distribution of  
5 changes in patients who met the outlier criteria. So  
6 the outlier criteria was a greater than 15 percent  
7 increase, and above the upper limit of normal. The  
8 active or placebo- controlled is on the left side, and  
9 on the right side with canagliflozin treatment groups.

10           And I think our conclusion from this is that  
11 there is not a notable difference in the distribution  
12 of more severe events with canagliflozin in those who  
13 met the outlier criteria.

14           With regard to the patients who had more  
15 severe hyperkalemia, it was pretty infrequent and the  
16 events that we saw were in patients who had multiple  
17 factors. The FDA presentation nicely noted that in  
18 patients on ACE or ARBs, the means were slightly  
19 increased. What we saw was that the patients who had  
20 the more significant values, for example we had one  
21 patient who was on aliskerin, an ACE inhibitor, and  
22 aldactone, and had CKD, and had a potassium that was

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1 over seven, that was some of the events that we saw.

2 We saw no changes in sodium concentration --

3 UNIDENTIFIED SPEAKER: (Off mic).

4 DR. STEIN: Hypokalemia. If we could pull  
5 the outlier criteria for hypokalemia, or for potassium,  
6 that will include hypokalemia. But just briefly, no  
7 there was no change in occurrence of outliers of  
8 hypokalemia.

9 DR. THOMAS: Actually, before you -- could  
10 you go back to the slide. Dr. Proschan, you had a  
11 comment?

12 DR. PROSCHAN: I'm not sure how to interpret  
13 that slide. I mean first of all, the scales are  
14 different, the Y-axis. And they're number of patients,  
15 not percentage.

16 DR. STEIN: Can you go back to the histogram  
17 please? Slide up.

18 DR. PROSCHAN: So that's number of patients,  
19 and they have different total numbers, and then the  
20 scales are different. So I don't know what to make of  
21 that.

22 DR. STEIN: I was really just trying to focus

1 on those patients who had more severe hyperkalemia. So  
2 if one looks above six, in terms of the distribution,  
3 as you note, there's more patients in the canagliflozin  
4 group who met the criteria. But the numbers of  
5 subjects with more severe elevations didn't appear to  
6 be particularly different.

7           We can analyze that by proportion. I think  
8 we also had an outlier analysis looking at those with  
9 more severe values and I think that had percentages. I  
10 think that's 2268, if we could pull that up, and that  
11 might address that. Do you have 2268 or perhaps I have  
12 the number wrong? Slide up.

13           So here's looking at the levels of potassium.  
14 So these are patients who have a potassium that's  
15 either greater than 6.5, and so this provides the  
16 incidence rather than just the distribution. The  
17 second row, greater than 7.0, and the bottom are  
18 patients who have occurrences who had more sustained  
19 hyperkalemia. And as you can see, the incidents didn't  
20 look to us to be notably different from patients with  
21 really clinically severe hyperkalemia, 6.5 or 7.0, and  
22 the values were not sustained for potassiums above 6.5.

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1                   So with regard to structural kidney disease,  
2   you asked about biomarkers.

3                   UNIDENTIFIED SPEAKER:   (Off mic).

4                   DR. THOMAS:   Just can I make a reminder?   So  
5   one thing is if when you are speaking, remember to have  
6   your microphone on.   And then if you're not speaking,  
7   to turn your microphone off.

8                   DR. STEIN:   So we're pulling that up.   So we  
9   were looking for hypokalemia I think, was the events of  
10   hypokalemia.

11                  DR. PALEVSKY:   Hyper.   If you have hypo too,  
12   but hyper is probably --

13                  DR. STEIN:   Hyperkalemia?   I'm sorry.

14                  DR. PALEVSKY:   Natremia.

15                  DR. STEIN:   Oh, I apologize.

16                  DR. PALEVSKY:   Hypo and hypernatremia.

17                  DR. STEIN:   So if you go back to that, we'll  
18   --

19                  DR. PALEVSKY:   And I wanted hypokalemia as  
20   well.

21                  DR. STEIN:   Okay, we'll pull that together.  
22   So if we could get the -- so this is for sodium.   Slide

1 up please. So this is looking at patients who met the  
2 criteria at any time, and for the last value. So the  
3 values below the lower limit of normal, with a greater  
4 than 5 mL equivalent decrease in the first row and the  
5 second row, are patients with events meeting  
6 hyperkalemia. And as you can see, there was a very  
7 slight increase.

8               These were consistently very minor, transient  
9 increases of patients who had values that were 152 or  
10 149. We saw minimal occurrence of values that were  
11 above -- 155 was very uncommon, and these were  
12 transient values. And the last (indiscernible) value  
13 is the last two rows, but I guess the point I'd make it  
14 was that the mean changed very little and very few  
15 meaningful outliers.

16               So for the potassium, slide up, with regard  
17 to the both increases and decreases. So the way we  
18 looked at it, just to orient you, is we looked at  
19 patients who met this criteria at any time during the  
20 study, and then for the last value that was still on  
21 study drug. And for the potassiums below the lower  
22 limit of normal, with a greater than 15 percent

1 decrease, that's shown there, which I think we thought  
2 was not meaningfully different.

3           For the increases, as you can see, there was  
4 no difference between the 100 in the non-canagliflozin  
5 group, with a slight increase in the 300 milligram  
6 group. But I showed you the distribution. Our  
7 interpretation was that these events tended to be  
8 fairly modest and not terribly more frequent with the  
9 300 milligram dose.

10           So with regard to the structural kidney  
11 disease, in our Phase II studies we looked at NAG,  
12 which is an issue because hyperglycemia and glucose  
13 infusion tends to increase NAG, so it's not a  
14 particularly good marker with this pharmacologic  
15 target. We also looked at beta-2 microglobulin. We  
16 did not have Kim-1, but we did look at beta-2  
17 microglobulin.

18           Slide up. This is from the Phase II dose  
19 range finding study. This was a 12-week study in  
20 patients with diabetes. The group sizes were  
21 relatively limited and we're showing the data here for  
22 the two clinical doses, the comparator and placebo.

1 And our interpretation was there was basically just no  
2 notable changes across groups, very small changes.

3 The biomarker that we took into Phase III was  
4 the urinary albumin to creatinine ratio because we  
5 thought it was also a useful and validated biomarker,  
6 both reflecting protocol glomerular and tubular injury.

7 And I showed you the data from that, which  
8 was consistently across all of the studies in which  
9 that was evaluated showing a reduction in patients with  
10 baseline albuminuria and no change in patients with  
11 baseline normal albuminuria.

12 DR. PALEVSKY: And I'd asked if you had the  
13 hemoglobin data.

14 DR. STEIN: Yes, we'll see if we can pull  
15 that out as well. That may just take a moment to find,  
16 so if we can get the distributions and the mean  
17 changes, that would be great. That's not the right  
18 one, so we'll come back to that. We'll pull that.

19 DR. THOMAS: Okay, so what we may do is,  
20 during the discussion, if you have that let me know.

21 DR. STEIN: Okay.

22 DR. THOMAS: At this time, I apologize --

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1 DR. CAPUZZI: Excuse me. I haven't had a  
2 chance and my light's been on a long, long time.

3 DR. THOMAS: So what --

4 DR. CAPUZZI: And I turn it off to be, you  
5 know, gratuitous. But I do want to say something.

6 DR. THOMAS: Doctor -- be brief, but you know  
7 the thing is we haven't been able to get to everyone  
8 because we do need to move on to the questions.

9 DR. CAPUZZI: But there's an important issue.

10 DR. THOMAS: Go ahead, but be brief.

11 DR. CAPUZZI: Okay. Now I just wanted to ask  
12 you, the -- there was this one line within the  
13 materials that were sent about an NMR LipoProfile  
14 change, which looked possibly problematic, and nothing  
15 else.

16 Now, did I understand at the end of the last  
17 session, that in the CANVAS trial it was shown that the  
18 plasma lipoprotein profiles were better, or that there  
19 were no untoward effects on these particles that would  
20 make them more, in any way, a problem for the  
21 development of the drug? I mean I'm not looking for a  
22 problem.

1 DR. STEIN: I can show you the results from  
2 that.

3 DR. CAPUZZI: No, I'm just -- please. There  
4 is not time for that. Were there any untoward effects  
5 from the -- or improved effects that really show that  
6 there are not an issue with the lipoproteins? We have  
7 to move quickly.

8 DR. STEIN: Well the particle changes that we  
9 saw was a relatively small increase in particle number.

10 DR. CAPUZZI: Right.

11 DR. STEIN: The increase was -- we saw a  
12 larger proportionate increase in the large particles,  
13 and a small proportionate increase in the small  
14 particles. There was no change in small particles at  
15 the 100 milligram, and about a three, five percent  
16 increase at the 300 milligrams. Does that answer your  
17 question?

18 DR. CAPUZZI: All right. That answers one  
19 part. But the other point I'm making is, were there any  
20 changes in plasma lipoprotein levels? That was one  
21 thing I wanted to know.

22 DR. STEIN: We did measure Apo protein B.

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1 DR. CAPUZZI: Right.

2 DR. STEIN: And the increase in Apo protein B  
3 was about half the extent of the increase in LDL  
4 cholesterol.

5 DR. CAPUZZI: Well they're both parts of the  
6 same animal, so that's not good. Is there anything  
7 favorable about the changes in lipoproteins?

8 DR. STEIN: We haven't measured other Apo  
9 lipoproteins. I mentioned that there's an increase in  
10 HDL, a decrease in triglycerides.

11 DR. CAPUZZI: All right. HDL cholesterol,  
12 right?

13 DR. STEIN: And total cholesterol change is  
14 very, very little.

15 DR. CAPUZZI: But not the part -- but the A1  
16 protein, the business end of it, just the HDL  
17 cholesterol?

18 DR. STEIN: No, we don't have A1 levels.

19 DR. CAPUZZI: Okay. You know I just wanted  
20 to make a remark. This is a very important issue with  
21 this drug and I'm just going to make a suggestion, and  
22 I really don't mean to sound in any way disrespectful.

1 But the CDC, 16 years ago, put out a green book, the  
2 laboratory measurements of lipids and lipoproteins for  
3 study, and for getting correct results. It doesn't say  
4 all that, but that's what it is, it's a green --

5 And it goes into great detail, not only about  
6 how you measure these, but how the patient is prepared,  
7 both in terms of their diet, the lack of other  
8 illnesses, not lying down. It's a very important thing  
9 to get correct data. I'm not trying to be obnoxious,  
10 right, so please. This should be done correctly.

11 And it's not just the measurements and the  
12 way you're measuring, it's how the patient's prepared,  
13 you know psychological or trauma or things like that.  
14 So I just wanted to make that suggestion for the rest  
15 of your studies. And I stop. Thank you.

16 DR. STEIN: Thank you. Questions to the  
17 Committee/Committee Discussion

18 DR. THOMAS: So we'll now begin the panel  
19 discussion portion of the meeting. Although this  
20 portion is open to public observers, public attendees  
21 may not participate, except at the specific request of  
22 the panel.

1                   And we'll start with question one. Based on  
2 the information provided in the briefing materials and  
3 presentations at today's meeting, please weigh the  
4 benefit risk profile of canagliflozin in the population  
5 of patients with type 2 diabetes and moderate renal  
6 impairment.

7                   In your discussion, consider and comment on  
8 the following: the impact of renal function on the  
9 glucose- lowering effect of the canagliflozin; the  
10 impact of canagliflozin on the risk of renal function  
11 deterioration; the clinical importance of observed  
12 volume and electrolyte related changes associated with  
13 canagliflozin use to the overall safety of this  
14 population; the clinical importance of the observed  
15 increased risk of genitourinary tract infection  
16 associated with canagliflozin use to the overall safety  
17 of this population.

18                   So just let us know if you have some comments  
19 on question one. Dr. Lewis?

20                   DR. LEWIS: So I'll begin the discussion I  
21 guess. So there's things about its use in the  
22 population of patients with decreased renal function

1 that I find disconcerting. Despite an increased area  
2 under the curve at the high dose, which I'm not sure I  
3 was totally -- my concerns about that in renal failure  
4 patients were totally assuaged by the fact that for 12  
5 weeks somebody got CANA 300 BID and pharmacokinetically  
6 it looked that would be okay if you had renal failure  
7 and got those kind of areas under the curve.

8           Despite that, there's less glucose lowering  
9 effects in them, so it's less efficacious, and yet  
10 there are as many or more side effects in them. So I  
11 think that we almost have to look at the risk benefit  
12 of it in them as a separate population, which a little  
13 bit impacts on how the next question I think is worded.  
14 Because I think it is quite different in them than it  
15 is in the general population. I hate for my patients  
16 not to be able to get a drug, so, and I hate it to be  
17 limited, but I'm concerned about it doing more harm  
18 than good in them.

19           The impact of it on renal function  
20 deterioration, I feel better looking at the histogram,  
21 that there isn't sort of a hidden -- like those mean  
22 decreases in GFR aren't reflecting a subpopulation that

1 are just having horrible things happen to them.

2           It's still almost hard to believe that it  
3 won't cause more acute renal failure associated with  
4 other illnesses, because they're relatively volume  
5 depleted. However, I would say that it is not the same  
6 as giving a diuretic to have an osmotic diuresis, but  
7 we put these people on diuretics all the time and they  
8 probably have some relative volume depletion. So I'm  
9 somewhat -- I'm less worried about that.

10           The only electrolyte issue I am a little  
11 worried about is I don't know that we thought enough  
12 about the impact of the hyperphosphatemia. I didn't  
13 hear anything about FGF-23 data or anything like that,  
14 which you would expect to go up with hyperphosphatemia,  
15 or with higher phosphorus' I should say, not  
16 necessarily hyperphosphatemia.

17           And the only other last comment I have on  
18 your last bullet point is obviously urinary tract  
19 infections are important in this population, as are any  
20 kind of fungal infection and all kinds of hygiene  
21 issues. In addition, I think it means that one of the  
22 most commonly used drugs, with this drug, may turn out

1 to be Diflucan, which is a cytochrome P450 drug, which  
2 this drug, at high doses, has potential to maybe do  
3 something with, which we didn't get addressed but I  
4 think should be addressed.

5 It is not one of the drugs that they  
6 specifically said wasn't going to interact with this  
7 drug. And I think that's an important thing to know  
8 that it won't, for the physicians who are going to use  
9 it. So I'll pause there for further discussion.

10 DR. THOMAS: Dr. Palevsky?

11 DR. PALEVSKY: So I'm going to basically  
12 agree with Dr. Lewis's comments. I'm not surprised  
13 that we see a lesser glucose lowering effect in  
14 patients who have underlying decreased kidney function.  
15 Since the mechanism is loss of glucose in the urine,  
16 and with a decreased GFR, the degree of glucose -- the  
17 magnitude of the glucose loss will be decreased because  
18 the filtered load will be proportionately lower.

19 I'm also concerned then that with a decreased  
20 benefit, that the risk profile may be altered. And I'm  
21 not sure that we have enough information -- this is  
22 already a population then that is at increased risk for

1 cardiovascular and other complications, and I'm not  
2 sure that we have sufficient information in that  
3 population. And I think that we're going to need, if it  
4 is a drug that then gets approved, that we're going to  
5 need post- marketing information, focused on that  
6 population.

7           I have relatively -- I'm relatively  
8 comfortable with the decline in kidney function that's  
9 seen. I do suspect that it is predominately  
10 hemodynamically mediated. One interesting question  
11 that I've not heard any, and don't know any information  
12 on, and couldn't find, is there are patients who have  
13 congenital glucosuria, presumably due to mutations in  
14 this transporter. And I don't know what the long-term  
15 history in terms of development of kidney disease is in  
16 them. My understanding is that it is an entirely  
17 benign finding, but any additional information from  
18 that natural occurrence of this would be I think  
19 helpful in considerations as to what the risk on kidney  
20 function is.

21           The electrolyte and volume depletion issues  
22 are not particularly disturbing to me, although there

1 may be a need for caution of use of other diuretics  
2 when this agent is being used to prevent clinically  
3 relevant hypovolemia. And in fact many of these  
4 patients have problems with volume overload underlying  
5 so that it may be beneficial from that standpoint. And  
6 I have no other comments beyond what Dr. Lewis said in  
7 terms of the GU infection.

8 DR. THOMAS: Sponsor, did you have a comment,  
9 a brief comment?

10 DR. STEIN: I was just going to briefly  
11 comment that -- two quick things. One is, in terms of  
12 SGLT2, deficiency states, the genetic deficiency, it's  
13 a wide range of urinary glucose excretion but some  
14 individuals with urinary glucose excretion in this  
15 range. And it's not a very well-characterized disease  
16 because it's infrequent, but there aren't reports of  
17 any untoward long-term effects. Occasional patients  
18 report in the literature with long-term follow-up  
19 without any report of a phenotype that implies a renal  
20 structural injury.

21 I was also going to just offer that I do have  
22 some additional renal safety information in the CKD

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1 patients, and be more than happy to show some of the  
2 outlier analysis and longer term follow-up if that  
3 would be helpful.

4 DR. THOMAS: Would that be helpful to you,  
5 Dr. Palevsky?

6 DR. PALEVSKY: Yes.

7 DR. THOMAS: Okay. Go ahead. While you're  
8 getting that slide up, Dr. Kaul, you had a question, or  
9 comment?

10 DR. KAUL: Did I hear them say that in the  
11 familial glycosuria there are no major problems? But  
12 we have numerous examples of genetically-mediated  
13 diseases, lipid disorders, where we don't have a higher  
14 risk of coronary artery disease as a glyceride  
15 disorder. And so I don't find that reassuring.

16 DR. STEIN: So let me just very quickly show  
17 two pieces of information. You were asking about  
18 longer term effects. Slide up. We do have data from  
19 the 3004. This is the dedicated study in subjects with  
20 a Stage 3 CKD, baseline is 30 to 50.

21 And what we saw at week 26, which I earlier  
22 showed, we see the same course, which is that there is

1 a continued attenuation with a rise in the eGFR back  
2 towards, not to baseline, in the 300 milligram group  
3 but to baseline or to the placebo group level with 100  
4 milligram group.

5           We've also looked at the outlier analysis.  
6 Slide up. I think you saw some data during the FDA's  
7 presentation regarding the any time value, so I thought  
8 it would also be useful to present the last values.  
9 Because we expected to see, with the any time values,  
10 the greater than 30 percent, because there's a  
11 reduction in eGFR, a shift to the distribution to the  
12 right, you get a lot more patients who are hitting the  
13 criteria.

14           But when you look at the last value, so this  
15 is the last on-study drug value, and this is in the  
16 1,000 patient pooled renal impairment dataset on the  
17 top, you can see that the numbers meeting the criteria  
18 of greater than 30 percent is not meaningfully  
19 different across the groups. The dedicated study is  
20 shown on the bottom, this is the DIA3004 study, where  
21 again I think supporting the same conclusions.

22           And I think you were also asking about

1 events. And I would just comment that the MACE-plus  
2 events were not increased in individuals with CKD. In  
3 fact, if anything, the trend was in the opposite  
4 direction.

5 DR. THOMAS: Any additional comments? Dr.  
6 Kaul?

7 DR. KAUL: I think I heard this morning  
8 somebody say that the prevalence of moderate renal  
9 impairment in diabetic population is somewhere around  
10 20 percent. And if that is the case, then the moderate  
11 renal impaired population in this dataset was  
12 underrepresented at only 10 percent of the total  
13 dataset.

14 And I have questions in my mind whether the  
15 40 to 50 percent attenuation of the glycemic efficacy  
16 in this population is clinically meaningful. You know  
17 if you have a quarter of patients achieving goal  
18 hemoglobin A1 less than seven, or (indiscernible)  
19 patients at the higher dose, is that clinically  
20 meaningful?

21 But I also heard in the presentation this  
22 morning that we're striving for a target of over 50

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1 percent. So I'm not quite sure whether the benefit  
2 risk balance in this underrepresented, moderately  
3 impaired renal function dataset is in favor of benefit.

4 DR. THOMAS: Yes, just --

5 DR. STEIN: I was going to offer that one of  
6 our experts that we have with us has expertise in the  
7 management of renal disease patients with diabetes.  
8 And if it would be useful, I could ask him to comment  
9 on the issue around clinical value because I think the  
10 context of limitations of the options in these patients  
11 has to be considered relative to the options in  
12 patients with more normal renal function. So if that  
13 would be useful, I could ask Dr. Bakris to come up and  
14 perhaps comment on that just briefly.

15 DR. THOMAS: Would that be useful to you, Dr.  
16 Kaul? Okay, as long as it's brief. Thank you.

17 DR. STEIN: Dr. Bakris?

18 GEORGE BAKRIS: Very quickly, I want to just  
19 agree with the comments that Julie and Paul made  
20 because they're right on the money. I do want to say  
21 that there's a review that is coming out in about two  
22 months in Nature Nephrology, that we just finished, on

1 looking at non-insulin glucose-lowering agents in  
2 people with advanced kidney disease and on dialysis.

3           There's a grand total of five agents, and  
4 most of them in reduced doses, half of whom either  
5 cause edema or hypoglycemia. So there really is a very  
6 small proportion of people -- a small proportion of  
7 drugs that is useful in these people. If you, because  
8 I do agree to a certain extent in terms of if you take  
9 the group below 45, I think Julia's on the money, the  
10 risk may outweigh the benefit there.

11           But if you take the group 45 to 60, you're  
12 getting 0.5 percent reduction, you add that to a little  
13 low-dose PIO and a little low dose of something else,  
14 and you may be in target if the patient's adherent with  
15 their diet. So I don't think you should throw the baby  
16 out with the bathwater. I think that's a very  
17 important point.

18           And, you know, it is about 30 to 35 percent  
19 of people that actually have advanced kidney disease,  
20 not on dialysis, but that is the number one cause. And  
21 this is a growing population in many ways, girth as  
22 well as other things. And I think that we need to

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1 offer to some options, as you heard actually from the  
2 public commentary. Thank you.

3 DR. THOMAS: Thank you. Any additional  
4 comments for question one? Dr. Palevsky?

5 DR. PALEVSKY: I just want to point out that  
6 in the elderly, the eGFR is decreased in large part  
7 because the formula includes age as a major component.  
8 So that if there wasn't availability of the drug based  
9 on eGFR of less than 60, it would exclude the drug from  
10 a large portion of the elderly population, who have  
11 aged into CKD Stage 3 with really near normal kidney  
12 function.

13 DR. THOMAS: And also one other thing I  
14 thought maybe one of our cardiologists or nephrologists  
15 might want to discuss this. Though I didn't see any --  
16 there is no data, any comments on the dosing in terms  
17 of what dose you might want to start out with because  
18 of the adverse side effects. Dr. Lewis?

19 DR. LEWIS: So the sponsor suggests that they  
20 start, if they have renal insufficiency, with the 100  
21 milligram dose. Since the 100 milligram dose is  
22 totally non-efficacious practically, everybody's going

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1 to get put on 300. And I don't think we have any  
2 information about why it would be safer to start at 300  
3 and then go to 300. I mean I didn't see any studies  
4 designed that showed that was safer or better. So you  
5 know I still am concerned about the risk benefit in  
6 people in the low GFR group. And I'm willing to say low  
7 GFR is less than 45 I mean, but the low GFR group.

8 DR. THOMAS: Any additional comments? If not  
9 I'll summarize the discussion so far. The drug seems  
10 to be less efficacious in glucose lowering as renal  
11 function decreases. We have no apparent reduction in  
12 side effects, so there potentially is an adverse risk  
13 benefit profile in people whose eGFRs are lower. And  
14 as a result, is the glucose lowering meaningful in this  
15 population?

16 And it depends how you break this down. If  
17 you were to look at the population in the study, which  
18 is an eGFR of 30 to 60, maybe the cut-off point is less  
19 than 45 or it's not as useful to have the medication or  
20 drug versus those who have a between 45 and 60.

21 The lowering that you see of the eGFR doesn't  
22 seem to be as worrisome after looking at the histogram.

1 There doesn't seem to be a defined subgroup that's at  
2 risk. And it's presumed that the lowering is based on  
3 hemodynamic changes. And I think one needs to see is  
4 that stable over time, and at least from the data  
5 shown, that seems to be relatively stable, or would it  
6 progress if people are using this for an extended  
7 period of time.

8           It's surprising that there are not more  
9 events of acute kidney injury due to the dehydration  
10 and volume depletion that's seen early on, which is a  
11 little surprising because of the way the drug is seemed  
12 to be work (ph). There is some concern about the  
13 increase in phosphorus, not for the sake of  
14 hyperphosphatemia, but because of the link to other  
15 diseases like cardiovascular disease. There weren't  
16 any measurements shown of agents that modulate  
17 phosphorus, like FGF-23, but that might be useful in  
18 follow-up studies.

19           There's also a concern about the effect of  
20 this drug in a population in terms of CVD, that's  
21 already risk for CVD. So if the drug is approved for  
22 use, in addition to cardiovascular trials that are

1 being done for the general population at risk, there  
2 may need to be more focused studies in this higher risk  
3 renal population.

4           There's a strong concern about the imbalance  
5 of genital urinary infections. Not only is there an  
6 increased amount of early infections, there's a high  
7 rate of recurrence. And one of the concerns as for the  
8 fungal infections, there'd be increased use of agents  
9 like fluconazole.

10           And fluconazole has P450 enzyme effects, and  
11 this would have interactions with potentially other  
12 medications that patients may be taking at the same  
13 time. So that will be a concern in terms of drug-drug  
14 interactions, not necessarily with this agent, but with  
15 other agents that patients are taking.

16           Finally, if you look at -- well not finally,  
17 but if you look at, there are individuals who have  
18 SGLT2 mutations. And though this is rare, there's no  
19 apparent understanding of any long-term complications.  
20 However this should not be reassuring.

21           As Dr. Kaul brought up, there are numerous  
22 examples of genetic disorders that seem to have no

1    apparent side effect, yet have pathogenic or  
2    pathophysiologic effects in patients without that  
3    mutation. And one classic example is  
4    hypertriglyceridemia. Isolated hypertriglyceridemia  
5    doesn't seem to have cardiovascular risk, however we  
6    know triglyceride elevations is a cardiovascular risk  
7    factor.

8                    If you look at the labeling in terms of if  
9    it's just eGFR, the elderly, by the nature of the  
10   formula and calculation, many elderly will have a low  
11   eGFR without actually having compromised renal  
12   function. So there should be some consideration about  
13   what's the best way to allow elderly patients who might  
14   be appropriate for this drug to take this beyond the  
15   eGFR measurements.

16                   And it's not clear if at the dose of at 100,  
17   you're really going to get any benefit, so what's the  
18   best way to start this drug. It was suggested by the  
19   sponsor, in the impaired renal population you start at  
20   100 and then potentially go to 300. But because of the  
21   efficacy, it's almost clear that everyone's going to be  
22   at 300, so there needs to be some further refinement of

1 the process of initiation of the drug and dose in the  
2 impaired renal population.

3 Is there any additional comments or  
4 corrections to what I said? Dr. Cook?

5 DR. COOK: Let me just add one other point  
6 about that starting dose of 100, in that in this  
7 population we also see that they have the greater  
8 problems with intravascular volume depletion at the 300  
9 dose. So if most patients are going to be up titrated  
10 quickly to the 300 dose, then that is the higher risk  
11 population for the intravascular volume depletion,  
12 which would be a concern.

13 DR. THOMAS: So add to that, to the comments  
14 about the intravascular depletion at the 100 versus 300  
15 dose. And Dr. Lewis?

16 DR. LEWIS: Can I make a clarifying comment  
17 to what you said?

18 DR. THOMAS: Sure.

19 DR. LEWIS: So eGFR just takes the serum  
20 creatinine and informs it with age, race and gender.  
21 So delta eGFR is delta creatinine in -- because  
22 people's race and gender generally don't change, they

1 don't age that much. Older people have lower muscle  
2 masses for any given creatinine. They actually do have  
3 a lower GFR and people do -- there's at least a body of  
4 literature to suggest many elderly people do lose renal  
5 function with age.

6 I think the comment that -- the point he was  
7 trying to make is not that older people wouldn't have a  
8 lower eGFR, but that it would eliminate a lot of older  
9 people if you eliminated them based on eGFR. However,  
10 a healthy elderly person is not going to have a GFR  
11 less than 60. So if you used the less than 45 cut off,  
12 I think the elderly who had relatively normal kidneys  
13 and had just aged would be okay.

14 DR. THOMAS: And that's what I intended but  
15 you said it much more eloquently so we'll go with your  
16 comments. Okay. We'll move on to question two.

17 In analysis of clinical fractures across the  
18 Phase III development program, a numerical imbalance  
19 not favoring canagliflozin was seen in the incidence  
20 and in the exposure-adjusted incidence of fractures.  
21 The disparity appears to be driven by low-trauma upper  
22 limb fractures and to a lesser degree by spine

1 fractures, with little differences in lower limb,  
2 pelvis or rib fractures.

3           Comment on the clinical significance of this  
4 finding on your overall assessment of safety. In your  
5 discussion consider the following: the relevance of  
6 observed changes in calcium, phosphorus, parathyroid  
7 hormone and 1,25 dihydroxy vitamin D levels; the  
8 relevance of changes to bone turnover markers; the  
9 relevance of the bone mineral density changes at 52  
10 weeks in the dedicated study in elderly individuals,  
11 DIA3010; the clinical importance of the bone and  
12 calcium metabolism-related effect associated with  
13 canagliflozin; the use to the overall safety of this  
14 population and in the renally-impaired population.

15           So if we have any comments or thoughts from  
16 the panel. So while people are thinking, I can get  
17 started. It's fairly well-known that with weight loss,  
18 whether by diet or other medications, or to gastric  
19 bypass, that you will see alterations in calcium  
20 metabolism. And you would also see effects on bone  
21 density.

22           Some of that is presumed to be the decrease

1 in weight. Actually the decrease is -- actually the  
2 bone density is less stress on the bone. And if you  
3 look studies that look at bone density after gastric  
4 bypass, you see a reduction in bone density.

5           So I think the question I have is, is this a  
6 limited effect. We presume that the weight loss  
7 plateaus, and if that's the case, then the potential  
8 bone density reduction should plateau as well. If the  
9 weight loss doesn't plateau, or there's an independent  
10 effect of the agent on bone density, then we can  
11 consider that would get worse.

12           So I think one year necessarily is not  
13 sufficient for follow up. And I think for a long-term  
14 study, whether this is pre- or post-marketing approval,  
15 probably we do need some type of long-term on fracture  
16 study. I think it's quite concerning that you're  
17 having potential risk but it's not clear that there is  
18 of fractures that are fragility fractures.

19           Now this is a population you would think that  
20 may get fragility fractures, but men at that age don't  
21 necessarily get them, though there is data that type 2  
22 diabetes, the population does have some increased

1 osteoporosis. So that would definitely need some type  
2 of follow up.

3           So the first one would be bone density, in  
4 terms of long-term follow up, and also long-term  
5 changes in calcium and vitamin D and parathyroid  
6 hormone. I don't think actually the magnitude of the  
7 changes is worrisome; it could be just related to the  
8 weight loss.

9           The bone turnover markers also seem to go on  
10 the line. You would see increased reabsorption  
11 markers. The one thing that's also related, which I  
12 didn't think we got into, is this population is also  
13 probably postmenopausal, but there could be some  
14 perimenopausal people and that might have some impact,  
15 though generally there was menstrualized (ph) women  
16 especially in the cardiovascular trial overall. But  
17 the bone density studies was in an elderly population  
18 so you presume they're postmenopausal.

19           The last thing is, related to this is, you  
20 know this is an agent that, unlike many other diabetes  
21 agents, we tend to think of a progression. We use an  
22 agent, then we stop it. We add another agent.

1           We go on to insulin. There are very few  
2 agents that we tend to keep, that are all medications  
3 for the entire course of someone's diabetes care.  
4 Metformin probably is one of the exceptions.

5           This agent is an agent potentially you could  
6 use throughout someone's diabetes care because of the  
7 mechanism of action. And the fact that there are  
8 individuals who are younger, who have type 2 diabetes,  
9 and though I don't think it's going to -- essentially  
10 in the label, there is always the potential, if one of  
11 our former panel members were here he probably would  
12 have brought it up, that it could be used in a non-type  
13 2 diabetes population.

14           And the concern I would have if alterations  
15 in bone density, is if you have young enough  
16 individuals, teenagers, 20-year-olds, they're  
17 developing peak bone mass, where does that leave them  
18 down the road? For short-term fracture risk, they're  
19 not going to have that.

20           But if they're on this agent for 5, 10, 15  
21 years while they're developing peak bone mass, and  
22 after the accretion of peak bone mass, will that lead

1 to earlier osteoporosis and fractures in their 40s and  
2 50s versus 60s and 70s?

3 So I think there's a lot of long-term follow  
4 up that has to be done. And not necessarily all that  
5 can be in a trial, so it probably should be registry  
6 based. Any other comments? Please.

7 DR. STEIN: I was going to offer two points.  
8 One is that we have done some analysis to look at the  
9 association with weight loss. I'll also say that we've  
10 consulted extensively with Dr. Bilezikian, who is here  
11 with us today, including on the question of the  
12 likelihood of progression of the bone overall density  
13 changes from the analysis we've done at week 52. And  
14 if the committee would find it helpful, I'd be more  
15 than happy to ask him to comment on that.

16 DR. THOMAS: Dr. Bilezikian, if you want to  
17 comment briefly on that, that would be fine. And  
18 specifically on the topic if the bone related changes  
19 would persist beyond the one-year follow up.

20 JOHN BILEZIKIAN: Bone would be the forgotten  
21 subject today. I'm John Bilezikian and I'm head of the  
22 Division of Endocrinology and head of the Metabolic

1 Bone Diseases program at Columbia. So the question of  
2 the long-term follow up is obviously relevant. But  
3 there's some short-term effects that we've all noted,  
4 and it certainly cannot be explained by changes in bone  
5 density.

6           Whether you use DEXA, the changes are so  
7 minimal as to be well within the precision of most of  
8 our instruments, but even if you look at the QCT data,  
9 where the changes are a little bit greater and we  
10 typically see more by QCT. But whether or not that's  
11 of concern, I honestly don't know.

12           But the finite element analysis of those high  
13 resolution images do not show any changes in bone  
14 strength. So taking that and the essentially less than  
15 dramatic changes in hormonal numbers, yes bone turnover  
16 markers go up and that may well be related to the  
17 weight loss, as the small change in bone density.

18           So we're left with an early imbalance in  
19 upper limb fractures, and that is perplexing. Those  
20 are very unusual places to be predominately fragility  
21 fractures. And the early course is also quite atypical,  
22 particularly if you're going to focus on bone turnover

1 markers and bone density, where you almost always see  
2 those changes first, and then you see the fracture  
3 events.

4               So there's really a mismatch here with regard  
5 to trying to put this all together. And I therefore  
6 think that the early imbalance is probably not related  
7 to bone density, to bone turnover markers, to metabolic  
8 parameters, or to bone strength. There must be  
9 something else. If there is something else, there may  
10 not be because it's an imbalance, it isn't a  
11 statistically significant change.

12              UNIDENTIFIED SPEAKER: If you could also  
13 comment on the likely time course past week 52.

14              JOHN BILEZIKIAN: Yes. So I would -- yes, we  
15 don't know of course. But my postulate would be after  
16 week 52, when weight loss is no longer an issue, that  
17 these curves will smooth out. That would be my  
18 prediction. And of course we will find that  
19 information out in time.

20              DR. THOMAS: Thank you. Actually, based on  
21 that, there are a couple other things I would also  
22 suggest, that may be of useful consideration. One is

1 we've seen, years after the approval of the TZDs, the  
2 increased fracture risk, and it wasn't your typical  
3 fractures as well. And once that was highlighted,  
4 there were additional mechanistic studies that were  
5 done looking at bone biology.

6           It wouldn't be unreasonable to suggest that  
7 some of those studies be done now, looking at bone  
8 progenitors. And it may not be unreasonable in a  
9 subpopulation to look at bone biopsies to see if -- I  
10 think once the weight loss phase is gone, and also to  
11 look at the early phase to see there's some changes  
12 that might be helpful in elucidating what's going on.  
13 Dr. Lewis?

14           DR. LEWIS: So I guess the last three words  
15 are in the renally impaired. And I would just say this  
16 is another example where the hyperphosphotemia and  
17 decreased 1,25 vitamin D are the big initial features  
18 of renal osteodystrophy in renal failure patients.  
19 Anyhow we consider that to be a really bad consequence  
20 of renal failure. And not only associated with bone  
21 disease, it's debilitating but cardiovascular disease,  
22 valvular heart disease, all kinds of things we think

1 are bad.

2           So this is another sort of example where, in  
3 this subpopulation, they're going to pay potentially a  
4 bigger price for this side effect of the medication,  
5 because it does two bad things that are bad for them  
6 anyhow.

7           DR. THOMAS: Any additional comments? Since  
8 I did most of the talking, I can't write and speak at  
9 the same time too, also. If you could just use my  
10 comments to summarize, plus Dr. Lewis's, that would be  
11 fine. Well people can disagree with me, that's fine.  
12 But okay, so we'll move on to question number three.

13           The cardiovascular risk associated with  
14 canagliflozin use was assessed in a prespecified meta-  
15 analysis of adjudicated cardiovascular events across  
16 nine Phase II and III clinical trials using a composite  
17 endpoint, MACE-plus, that combines cardiovascular  
18 death, non-fatal myocardial infarction, non-fatal  
19 stroke and hospitalization for unstable angina.

20           Based on the information provided in the  
21 briefing materials and the presentations at today's  
22 meeting, please discuss the following: whether results

1 based on the pre-specified Cox proportional hazards  
2 model are reliable; your level of concern regarding the  
3 apparent imbalance not favoring canagliflozin in early,  
4 less than 30 days, MACE-plus events observed in the  
5 dedicated cardiovascular outcomes trial, DIA3008; the  
6 divergence of risk estimates for the components of  
7 MACE- plus in the prespecified meta-analysis in which  
8 the hazard ratio for nonfatal stroke exceeds 1.0, while  
9 the other components are below 1.0; the clinical  
10 relevance of the observed changes to blood pressure,  
11 weight and low density cholesterol levels toward  
12 informing overall cardiovascular benefit risk  
13 associated with canagliflozin use. Dr. Brittain?

14 DR. BRITTAIN: Well I'm pretty comfortable  
15 with the overall hazard ratio estimate. Even if there  
16 is some non-proportionality in the hazards, I don't  
17 think it's very great. And even if it is, it's still  
18 going to be a pretty good measure of the overall  
19 treatment effect. So I'm not that concerned,  
20 particularly since a number of sensitivity analyses  
21 were considered. For example, in the non-CANVAS  
22 studies, the results look quite good.

1           And in the CANVAS studies, even though we do  
2 have that concerning first 30-day period, once that --  
3 you know, the survival curves turn around. And not  
4 only cut -- you know converge, they seem to -- there's  
5 some suggestion that there may even be a possible  
6 advantage at six weeks, just a suggestion, I mean six  
7 months, just a suggestion of that. But when you put  
8 all that together, I'm pretty comfortable that the  
9 hazard ratio estimate is a fairly reasonable measure of  
10 the treatment difference.

11           I'm not really sure what to make of the first  
12 30 days. Again, because the survival curves do turn  
13 around, so I'm not -- you know, even if that were true,  
14 that there was some excess at the very beginning, if  
15 the survival curves do turn around, I'm not sure what  
16 the importance of that is. And so I don't know.

17           And with respect to the stroke, I guess the  
18 fact that the -- to me, at least it's comforting that  
19 the non- fatal MI and the fatal cardiovascular events  
20 are going the other direction makes the fact that the  
21 stroke exceeds one, with a confidence interval around  
22 it, less of a concern. And I think, you know, if it

1 had been the cardiovascular death that was exceeding  
2 one, I would be more worried.

3 DR. THOMAS: Dr. Hiatt?

4 DR. HIATT: So I'm a little more  
5 uncomfortable with whether there's a proportionality  
6 throughout, on the MACE events. I mean the first point  
7 is that the totality of the evidence should drive the  
8 thinking and the confidence intervals around the data  
9 so far are below 1.3 of the upper bound.

10 So that's, you know, it's clearly below the  
11 guidance threshold. So one could easily stop there and  
12 conclude that there really is no cardiovascular signal  
13 at all. But I do think that the divergence of  
14 events, early versus late, at least raises a signal of  
15 concern but it's certainly not definitive.

16 And so then the question would be is that  
17 just a numeric imbalance that occurred by chance, or is  
18 there some mechanism that could maybe drive that? And  
19 so I was struck by the clustering of hypotensive  
20 events, hypovolemic events that occurred early.

21 I recognize the sponsor and the FDA went to  
22 lengths to demonstrate that there was no clear

1 relationship. But I'm not sure you could easily find  
2 one. You know, I'm not sure that the hypotensive event  
3 was necessarily at the same time as the CV event. But  
4 certainly the fact that these two things were occurring  
5 does raise concern.

6           So then you ask well, the sponsor's also made  
7 a point that lowering blood pressure with this agent is  
8 a good thing. And so I think back actually eight years  
9 ago to a cardio renal meeting where we reviewed anti-  
10 hypertensive agents and came to the conclusion that  
11 blood pressure drugs that lower blood pressure by and  
12 large prevent CV events.

13           And it turns out that different agents, using  
14 different mechanisms, get there through different  
15 mechanisms and maybe change components of the composite  
16 slightly differently, but overall there's a benefit.  
17 But we didn't really take on the issue of lowering  
18 blood pressure by osmotic diuresis, which I think is  
19 kind of a non-physiologic way to lower blood pressure.

20           And therefore, if you look at that mechanism  
21 compared with the adverse event profile and the time to  
22 first event being quite striking in the first 30 days,

1 and then look at least a numeric imbalance in the early  
2 first 30 days, it just raises concern to me that I  
3 think we can't ignore.

4           So are there other examples of treatments  
5 that do that? And there are. I mean there are things  
6 like bariatric surgery that early on you have excess  
7 death, in the perioperative period, but then as the  
8 treatment, surgical treatment takes hold, then those  
9 curves reverse quite clearly. And that's true for some  
10 other procedures like carotid endarterectomy where you  
11 know you take a hit early because the procedure you  
12 know has a perioperative risk. But once that risk is  
13 resolved, then the benefit accrues over time.

14           So the question here is are patients really  
15 taking a hit or not? I mean I can see where a patient  
16 with cardiovascular risk, particularly in the CV  
17 outcomes trial, would have a higher risk of hypovolemia  
18 and hypotension than a healthy younger person. And so  
19 the fact that pooling of the data from those other  
20 trials didn't show that doesn't surprise me.

21           The other piece of this puzzle I think is the  
22 late risk. And you know the lipid changes I think are

1 fairly, I'm not going to call them striking, but I  
2 think that there's no doubt in my mind that if you look  
3 at the LDL, the Apo B changes, that there's really an  
4 adverse effect on lipids here. And so this non-  
5 proportional hazards curve looks like it's kind of  
6 coming back down again at the end, and of course that's  
7 because there's not many events out there and the  
8 certainty goes away.

9           But you know it does sort of make one wonder  
10 if we're not sort of looking a little early here and  
11 wondering what the cumulative total risk assessment  
12 might look like when the CV outcomes trial's actually  
13 completed.

14           So that I think there's two components of  
15 this risk equation that make me concerned. The early  
16 hypovolemic, hypotension risk, paired with this sort of  
17 imbalance, and then the late risk which has not been  
18 fully evaluated because, in terms of changing lipids,  
19 you know if we lower them with statins, the curves  
20 don't separate right away. And so if we raise them by  
21 some other mechanism, I don't know how long it's going  
22 to take to see that consequence. So I think the

1 dataset's a little incomplete.

2           And I think these markers that we're seeing  
3 here at least make one pause for concern. But you  
4 know, the totality of the evidence, the point estimate,  
5 the confidence interval, obviously that's very  
6 reassuring. But I'm not completely satisfied that  
7 that's the complete story today.

8           DR. THOMAS: Dr. Proschan?

9           DR. PROSCHAN: I'd like to actually suggest a  
10 correction on bullet number three. It talks about the  
11 hazard ratio for non-fatal stroke exceeding one. It  
12 was my impression that that was, that 1.46 compared was  
13 all stroke. If it's just non-fatal stroke, then I say  
14 that analysis doesn't make sense because then you'd  
15 have to sensor fatal stroke, which would be ridiculous.

16           So I think that corresponds to all stroke,  
17 right? Fatal and non-fatal. The sponsor had F and --  
18 you know, made it look like it was fatal and non-fatal.

19           DR. THOMAS: Dr. Guettier?

20           DR. GUETTIER: That's correct, it's actually  
21 all strokes.

22           DR. PROSCHAN: All strokes, okay good. Okay,

1 so with respect to the business about the first 30  
2 days, I think this is a really tough thing to try and  
3 figure out. Because even if you had specified in  
4 advance, I think there might be a difference in the  
5 first 30 days versus beyond that, then the P-value is  
6 still not significant, or at least you know it's  
7 questionable.

8 But the fact that you didn't do that, the  
9 fact that you looked at the curves and looked for  
10 places where it might seem to go the wrong way for a  
11 while and then look better, it makes it much more  
12 difficult to interpret any kind of P-value.

13 So for example, when you look at the curve  
14 and you say okay, look at these first 14; 13 of them  
15 were in the drug group. You know, you're sort of  
16 picking the worst spot.

17 So it's very analogous to monitoring a  
18 clinical trial after every new endpoint, computing your  
19 P-value after every new event, and then looking, is  
20 there any place for which that is going the wrong  
21 direction a significant amount?

22 And if you have a large enough trial, there's

1 actually a pretty high probability of finding at least  
2 one spot where it seems to be going the wrong  
3 direction. Yet even though you know you're looking for  
4 this place where it goes the wrong direction, it still  
5 doesn't come out significant by conventional means.

6           So that tells me that you know the evidence  
7 is by no means convincing that it's going the wrong  
8 way, that that going the wrong way is real. However,  
9 of course, you know I can't say it's not true, it's  
10 just that the evidence to me is not really that  
11 compelling, especially when you consider you know the  
12 2:1 randomization that would make 13:1 otherwise sound  
13 really striking.

14           But even if you grant that, even if you grant  
15 that there is a real difference, early versus late, I  
16 still think it's reasonable to sort of combine those,  
17 look at the overall hazard ratio, and conclude that  
18 things are pretty good.

19           As far as the stroke, you know that is  
20 disturbing and I don't know whether that's real or not.  
21 But I think if it were real, I think you would tend to  
22 see the same thing with some of these other

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1 cardiovascular outcomes. So I'm largely satisfied with  
2 the cardiovascular events, not completely of course,  
3 but largely satisfied that they've shown what they need  
4 to.

5 DR. THOMAS: Dr. Knowler?

6 DR. KNOWLER: Well I'll be brief because what  
7 I wanted to say has been said, but I did want to  
8 comment on the proportionality since I had raised  
9 questions about that. I basically completely agree  
10 with what Dr. Brittain said, and I won't repeat that  
11 argument. It's not a concern for me.

12 From the data we've seen, I see no concern  
13 about cardiovascular disease. But with the lipid risk  
14 factors, I certainly am concerned that in the long run  
15 something might develop, and so I think the story's not  
16 finished yet.

17 DR. THOMAS: Dr. Kaul?

18 DR. KAUL: Yeah, with regards to the first  
19 issue, I agree with the expert statisticians. I don't  
20 think that's a major issue. I have some degree of  
21 discomfort in trying to figure out what to make of this  
22 cardiovascular outcome data. I mean the fact that we

1 don't see this early hazard in the non-CANVAS dataset  
2 can easily be explained on the basis of what Dr. Hiatt  
3 just mentioned, that the CANVAS trial population is a  
4 higher risk population. It's particularly prone to  
5 some of these hemodynamic events that were not captured  
6 because the first visit was at six weeks and it might  
7 have -- they may easily have missed that.

8           In terms of the hazard ratio, they appear to  
9 meet the criteria, but I was more interested in looking  
10 at what the clinical impact of those data are in terms  
11 of the totality of data. I would have liked to have  
12 more information about what was the clinical impact of  
13 these stroke event rates. What if most of these  
14 strokes are disabling, and what if most of the MI  
15 benefit is driven by biomarker criteria of MI, of  
16 questionable clinical relevance? And I was not able to  
17 make that balance in my head.

18           Yes, there is 16 out of the 37 cardiovascular  
19 events were contributed by fatal MI and fatal stroke,  
20 which is less than 50 percent. So where are the other  
21 cardiovascular evidence coming from? So I had some  
22 difficulty in sort of formulating.

1           There is uncertainty. The follow up, I would  
2 like it to be longer, two-year follow up to see what  
3 would be the impact of the lipid profile. Is this LDL  
4 elevation something of potential concern or not?

5           And then I have concerns about the trial  
6 design. If I heard the sponsor say it correctly, CANVAS  
7 has two sets of endpoints. There is a primary  
8 composite endpoint for the prespecified combined or  
9 pooled MACE meta- analysis, which is the MACE-plus  
10 endpoint. And then the original endpoint was a  
11 stringent MACE endpoint. And how do you control for  
12 the type one error?

13           I mean in the briefing document, on Table 39,  
14 we see the alpha errors presented, but that's  
15 presumably for the MACE-plus meta-analysis endpoint.  
16 How do you control for the original primary endpoint,  
17 which was the MACE? So I have issues with that.

18           The other issue I have is that, and I think  
19 the FDA will have to really think long and hard about  
20 this, how do you allow an interim analysis to impact on  
21 your regulatory decision-making? And the reason why I  
22 say that is because let's say the drug gets approved.

1                   How do you ensure that the trial integrity is  
2 preserved? How do you make sure that the crossover is  
3 minimized? What if after the drug gets approved, the  
4 patients who are randomized to the control arm want to  
5 be on the active treatment? That will sort of shrink  
6 the differences and bias the upper bounds towards the  
7 null, and make the drug look safe from a cardiovascular  
8 point of view.

9                   I think -- I'm sure the FDA is already  
10 deliberating this issues and I acknowledge that the  
11 guidance document is a work in progress and that it's  
12 through these interactions or deliberations that we  
13 will make more progress in terms of what advice to  
14 offer to the sponsors. So those are some of the  
15 concerns that I have in regards to the cardiovascular  
16 dataset.

17                  DR. THOMAS: Dr. Savage?

18                  DR. SAVAGE: I'll try to be brief because I'm  
19 really repeating some of the things that have already  
20 been said. But I basically agree with what Dr. Hiatt  
21 said, I have concerns about the fact that although the  
22 overall cardiovascular data look reassuring, you're

1 making an educated guess if you actually draw final  
2 conclusions based upon that.

3 I think that clearly some long-term follow up  
4 is necessary to particularly find out whether there's  
5 any adverse effect of the lipid changes that have been  
6 documented. And I might mention that about 15, 18  
7 years ago, when rosiglitazone was first coming out,  
8 notice was taken of the fact that LDL cholesterol was  
9 elevated in patients on that drug, and the claim was  
10 made that the particle sizes and so forth were such  
11 there wasn't anything to worry about.

12 So I agree with some of the comments that  
13 have been made, that in this particular case it looks  
14 like the risks are not as -- you know there are some  
15 reassuring data here also. But there's no doubt that  
16 there needs to be a long-term follow up.

17 And the issue that Dr. Kaul raised as to  
18 these designs and whether this particular design of the  
19 way the trials are being done may raise some design  
20 issues. I think I'd leave that up to the people with  
21 more expertise in study design to deal with.

22 But I would like to point out that in a way,

1 the fact that there is an ongoing trial right now means  
2 that we'll have better answers to some of these  
3 questions within a few years.

4           If we were in this situation today, and the  
5 other trial had stopped and someone had just -- and the  
6 company had to mount a whole new trial and go on for  
7 several more years to get five-year data, it would be  
8 eight or 10 years before we'd have the data. And this  
9 way we'll get the data more quickly.

10           So, you know, I think the FDA people have to  
11 weigh all the pros and cons of the design issues, but  
12 this is an example of where the attempts to figure out  
13 how we could design something that wouldn't block the  
14 development of diabetes drugs, because of extremely  
15 high cost to get them initially approved, could pay  
16 off, that we've got something in place.

17           DR. THOMAS: Dr. Brittain, you had a comment  
18 on that?

19           DR. BRITTAIN: Yeah, I just wanted to make  
20 sure -- I want to get the FDA perspective on. You  
21 know, the CANVAS trial's ongoing. And they said they  
22 were going to wait until they have 500 -- go until they

1 have 500 events. What would be, if the drug's approved  
2 in the short term, what is the process then as that  
3 data accumulates? If, in fact, the long-term data do  
4 not look good.

5 DR. PARKS: So I'll start off and then see if  
6 Dr. Rosebraugh or others members of the team want to  
7 weigh in. Currently how it stands with the  
8 cardiovascular, the CV guidance for diabetes drugs, is  
9 that they need to first provide us the reassurance of a  
10 higher threshold of risk. Again, I've mentioned  
11 earlier that this sets up a reasonable bar for these  
12 companies.

13 It should be, going to question four, is that  
14 if we -- if you think that there is really no concern  
15 here about them having been able to successfully  
16 discharge that, or rule out, exclude that risk, then  
17 the expectation is that, after approval, they still  
18 have to demonstrate that there's an unacceptable risk  
19 at a lower risk margin, the 1.3. And that can be done  
20 in several ways.

21 Now you probably noticed we did not ask you  
22 the question on whether -- what source can be, form the

1 basis for them to exclude a more conservative risk  
2 margin? I think that everything that has been raised  
3 at the table here today regarding the interim analysis,  
4 the cholesterol, the increase in the LDL cholesterol,  
5 the partial unblinding of this trial, these things have  
6 been considered by the agency internally as well.

7               So that is something that we have to consider  
8 as to what is the level of evidence that they must  
9 provide us to be able to reassure us of not having at  
10 least a 30 percent excess in cardiovascular risk.

11               DR. THOMAS: Dr. Capuzzi?

12               DR. CAPUZZI: Yes. I just have one minor  
13 point to make. Aside from insulin, this is the only  
14 medication class that has an action without involving  
15 insulin. I don't know if anybody else can think of  
16 one, but this is the only one I could think of one.

17               And it actually might have more utility in a  
18 patient that needs therapy but has more preserved renal  
19 function. Because the kidney, as everybody knows, is  
20 like an endocrine organ, it modifies things, it reacts  
21 to aldosterone. We have no idea what the whole, it's  
22 cortex (indiscernible). So I think that's an easier

1 way to go, but that's a little, you know, different.

2 Okay, it's a thought.

3 DR. THOMAS: Dr. David Cooke?

4 DR. COOKE: The only brief comment I would  
5 make regarding the fourth bullet point is this issue of  
6 predicting the ultimate cardiovascular outcome is  
7 complicated. There is this relatively modest increase  
8 in LDL, but it's potentially balanced by some  
9 beneficial effects of the decreased blood pressure,  
10 decreased weight, rising HDL.

11 So I would agree that ultimately we have to  
12 wait and see. But currently, without a concerning  
13 signal, I think I'm not bothered by the cardiovascular  
14 risks at this time.

15 DR. THOMAS: Dr. Lewis?

16 DR. LEWIS: I think you must have read my  
17 mind, because I don't remember putting my hand up. But  
18 I do have a question for the FDA, because I'm not sure  
19 I still understand the answer to it.

20 What are the precautions that have been taken  
21 to make sure that the people in CANVAS, once the drug  
22 is available, don't cross over to active drug? And

1 what are the agreements, if any, should the ultimate  
2 results of CANVAS either not be done, because you just  
3 can't get the results because too many people crossed  
4 over, or they're negative?

5 Will the drug -- I mean do you have an  
6 agreement about what would result in removing the drug  
7 from the market at that point?

8 DR. PARKS: There are a lot of questions in  
9 there. Now the first one you're touching on, that is a  
10 very, very complex issue. I'm not going to speak about  
11 CANVAS specifically; it's more of in general. What do  
12 you do with these ongoing cardiovascular outcomes trial  
13 where, you know, we're starting to see more of the  
14 agency considering regulatory decisions based on  
15 interim data, and how to protect the integrity of that  
16 ongoing portion.

17 And there are a lot of things that are being  
18 discussed with drug companies, within the agency, with  
19 our legal folks. The issue here is a matter of agency  
20 having to be transparent in our decision on whether a  
21 product has been deemed safe and effective for how we  
22 intend to label it, but at the same time, understanding

1   that sometimes the need to be transparent to the public  
2   may actually also affect our ability, the public's  
3   ability, the scientific community's ability, to be able  
4   to continue to get very good data.

5               These studies are going to be required post-  
6   marketing studies. So to that extent, that's where we  
7   have the regulatory teeth to ensure that they get us  
8   that information. I mean if they don't get that  
9   information because of complacency or whatever on a  
10   company's part, then there are penalties that can be  
11   applied.

12              If it's a matter of that there's been some  
13   impact, negative impact on the conduct of the trial  
14   because people have some erroneous preconceived notion  
15   on a limited amount of information, that is going to be  
16   problematic.

17              So these are issues -- I don't think we can  
18   resolve it here today, but if I can provide some  
19   reassurance to the panel member, these are active,  
20   ongoing discussions within the agency. Anywhere from,  
21   you know limiting the amount of information that can be  
22   provided at the time that we make a decision, or being

1 fully transparent and sharing all the information but  
2 coming down very strongly with any of our decision  
3 memos saying you know one should not make any  
4 definitive conclusions on the overall cardiovascular  
5 safety of this product to start impacting how one  
6 behaves, or how one conducts a clinical trial. That  
7 may do it. This is very much uncharted territory.

8           And then, at the end of the day, one also has  
9 to remember that-- you know the issue is that while the  
10 information may be -- the end results may be shared, if  
11 the trial is still indeed double-blinded and  
12 controlled, is that a level of reassurance? So I don't  
13 know if I've answered your question. The only thing I  
14 can say is that we have been thinking about this  
15 significantly.

16           DR. LEWIS: Well I guess maybe the company  
17 knows the answer to it, too. Like I'm wondering --  
18 like say it got approved today. That means that -- it  
19 doesn't mean that tomorrow someone could go to a  
20 pharmacy and get this medicine.

21           So there is this time lag that's sort of  
22 inevitable while they do all the stuff they have to do

1 and market and whatever. How close will be to the end  
2 of the CANVAS trial before a patient could go to a  
3 pharmacy and get this drug? Do we know that?

4 DR. THOMAS: Sponsor?

5 DR. STEIN: So just as a note, the trial  
6 remains double-blinded. And we are very carefully  
7 tracking the discontinuation rate, which of late has  
8 come down substantially. We're making tremendous  
9 efforts to try to avoid losing subjects.

10 Obviously, we don't anticipate that we would  
11 have any meaningful loss of subjects based upon the  
12 release of the information, but we'll track that and  
13 obviously have to discuss with the agency the  
14 implications if that were to occur. But presently the  
15 current discontinuation rate accruing is quite small.  
16 And again the trial remains double-blinded.

17 With regard to the time frame, the trial had  
18 a prespecified analysis which we've conducted in  
19 January. The next prespecified analysis would be -- we  
20 expect to be in 2015, based upon the current accrual of  
21 events with 500 events.

22 The trial will continue at least to that time

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1 point, and then would potentially end at that point if  
2 the next step was met, which is to demonstrate the 1.3  
3 upper bound.

4 DR. THOMAS: Dr. Kaul and then Dr. Rasmussen.

5 DR. KAUL: You know I just wanted to respond  
6 to Dr. Parks' statement. I agree with everything you  
7 said. But enrolling in a trial with the fore knowledge  
8 that the drug has already been approved is one thing.  
9 And enrolling in a trial where the drug is not approved  
10 and then you find out that there is a suggestion of  
11 benefit, it's very tempting for the patients to cross  
12 over to the, quote unquote, beneficial drug. And I  
13 think we should not underestimate the impact it will  
14 have on what the sponsor and the agency is trying to do  
15 is rule out unacceptable cardiovascular risk.

16 DR. THOMAS: Dr. Rasmussen?

17 DR. RASMUSSEN: I just wanted to make sure  
18 that we all understand that without knowing details of  
19 the protocol, I'm fairly certain that it's prespecified  
20 that patients are not allowed to choose other SGLT2s,  
21 or, if it was approved, canagliflozin.

22 DR. STEIN: That's correct.

1 DR. THOMAS: Can you use the microphone  
2 please.

3 DR. STEIN: Just to be clear, it remains  
4 double- blinded and there's no opportunity for patients  
5 to switch from one treatment to another. There's no  
6 allowance for other SGLT2 inhibitors. Patients may be  
7 treated, or expect to be treated, maximally to standard  
8 of care in this trial.

9 Maximal glycemic control on top of  
10 canagliflozin or the match to placebo, and of course  
11 aggressive other management of cardiovascular  
12 endpoints. But there is no opportunity for patients to  
13 add an SGLT2 inhibitor. If they were to take  
14 prescribed canagliflozin or prescribed any other agent,  
15 they would, in that class, they would have to be  
16 discontinued.

17 DR. THOMAS: Ms. Killion?

18 MS. KILLION: Yeah, I just wanted to respond  
19 also to Dr. Parks' comments. The, well that's not the  
20 word I want to use -- the adoption of a CV risk  
21 assessment for a drug, for diabetic drugs, it makes for  
22 a very complex world when it comes to drug approvals.

1                   And as a patient, it's been a concern of mine  
2   for some time that, you know that this is -- that we  
3   have to be very careful not to overburden the research  
4   and development process because we all know that we  
5   need new and better drugs for diabetics.

6                   And if we hold out the approval of drugs  
7   until the conclusion of long-term cardiac risk  
8   assessments, that's going to stall and it's going to  
9   chill development, and we can't have that as a diabetic  
10   population.

11                  So, I have empathy for the FDA, and you're  
12   trying to balance this and to work with the sponsors to  
13   make sure that these issues do not adversely impact  
14   patients in an overabundance of caution. But you know,  
15   that said, we have to be safe, but we also have to be  
16   reasonable and serve the needs of patients.

17                  DR. THOMAS: Dr. Hiatt? Dr. Proschan?

18                  DR. PROSCHAN: I just didn't quite understand  
19   that last statement about discontinuing patients who  
20   take something else. I mean we don't usually do that  
21   in clinical trials.

22                  DR. THOMAS: So if the sponsor just wants to

1 clarify that.

2 DR. STEIN: I was just indicating that we  
3 don't allow patients to take those agents. We haven't  
4 had, and we don't expect to see any of that occurring  
5 during the trial. We've been very aggressive at having  
6 the investigators maintain patients in this trial, and  
7 to continue to obtain follow up on the patients.

8 And so what I was saying is that we don't  
9 allow -- the protocol specifies that they would not be  
10 allowed to take another agent. I don't expect that to  
11 be an issue at all in the trial.

12 DR. KAUL: You know, for intention-to-treat  
13 analysis is going to be impacted. Your protocol, per  
14 protocol analysis is going to be preserved if you do  
15 what you just said. But the intention to treat  
16 analysis is going to be -- I mean there are numerous  
17 examples.

18 Just a recent example that comes to mind is a  
19 chemo therapeutic agent that was approved for renal  
20 cell carcinoma. I think it was a multikinase  
21 inhibitor, sorafenib, approved on the basis of a  
22 surrogate endpoint. And under subpart H, the patients

1 then crossed over. And when the final results came  
2 out, there was no evidence of any benefit. So there  
3 are many other examples. So one has to preserve the  
4 integrity of the dataset.

5           And you know, I mean you have to weigh the  
6 pros and the cons. As you correctly mentioned, you  
7 don't want to overburden the development and the  
8 introduction of these potentially beneficial drugs.  
9 But there's a price to be paid and one has to be aware  
10 of that. How can you minimize that error?

11           DR. THOMAS: Dr. Knowler?

12           DR. KNOWLER: I'll just add to this comment.  
13 Once a drug is approved, you either -- I mean if you  
14 say you will not allow anyone to go on that drug, that  
15 simply means you're abandoning the intention to treat  
16 principle, which is not good.

17           You can't stop someone from getting the drug  
18 from their doctor. You cannot provide it yourself, but  
19 you can't stop them from getting it outside.

20           DR. THOMAS: Any additional comments?  
21 Otherwise, I'll -- Dr. Rasmussen?

22           DR. RASMUSSEN: I'll just comment to that.

1 Fortunately, within the diabetes field, there are a lot  
2 of other alternatives. So it's fairly easy, in a  
3 protocol, to prespecify, please choose something else  
4 for the integrity of the trial.

5 DR. THOMAS: All right, I will try and  
6 summarize this, and probably I'll have a few  
7 corrections from the panel.

8 Overall, the concern about the proportional  
9 hazards model seems to be less. For one reason is that  
10 there have been some sensitivity analysis that have  
11 been done and additional data analysis that suggests  
12 that it seems to be reliable enough to make some  
13 interpretation of what's happening.

14 The data seems to be fairly believable and  
15 actually has a value of less than 1.3, and really we're  
16 looking at a value of 1.8 for this initial analysis.  
17 If you look at the concerns about the 30-day changes in  
18 risk, it's not sure what's really happening there  
19 because there are a lot of changes that are going on,  
20 that have been mentioned throughout the day, including  
21 vascular changes such as dehydration.

22 There are changes in electrolytes. And none

1 of these have been specifically linked to why there  
2 might be this early increase in events in the treatment  
3 group, but there's an uneasiness from some of the panel  
4 members that maybe something is going on.

5           However, this was not a prespecified  
6 analysis. And if you were to do this -- if you were to  
7 prespecify it, you'd have a greater chance of actually  
8 making interpretations of this data if it's useful, and  
9 it wasn't significant.

10           If you were to do the data analysis, you  
11 could potentially take any clinical trial, look through  
12 the data, and pick a 30-day or 60-day period where  
13 there might be differences in the outcome, whether it's  
14 favorable for the agent or negative for the agent. So  
15 it's probably not a good way of looking at the data.

16           The concern of course is in the first 30  
17 days. As we know from the surgical literature, there  
18 are many examples of surgical procedures, carotid  
19 endarterectomies, gastric bypass surgery, where  
20 there's a short-term increase in mortality, but there's  
21 a long-term benefit. And what we don't know is that  
22 in the future, is there really a short-term increase in

1 mortality?

2                   And I'm going to add this in, is there a  
3 specific subgroup, which is not identifiable at this  
4 time, that's at highest risk for this? Or is this just  
5 a red herring and we'll see a long-term benefit? That  
6 probably still has something to be answered from a  
7 long- term trial.

8                   What's the risk of the stroke issue? There's  
9 a couple of opinions that were floated by the panel.  
10 One is that the other components of MACE-plus were  
11 favorable. The point estimate was less than one. The  
12 hazard ratios were also within guidance. So people,  
13 even though there's an increased stroke confidence  
14 intervals, felt a little more reassured that the other  
15 ones are going in the right direction.

16                  I will just throw out a comment that stroke  
17 is actually kind of concerning in the sense that we  
18 make an assumption that MACE and MACE-plus had all the  
19 components going in the same direction. And it's clear  
20 there are several clinical trials where that is not the  
21 case. The one, of course, I'm most familiar with is  
22 the one I was part of, which was the ACCORD trial.

1           In the ACCORD blood pressure trial, the  
2 primary outcome was not significant, but the  
3 prespecified secondary outcome that looked at stroke  
4 and the other MACE components, stroke was actually  
5 decreased in the intensively treated blood pressure arm  
6 versus the other components were neutral or tended to -  
7 - actually had no benefit.

8           So, in that case, it was a favorable benefit  
9 on stroke, though it was a secondary endpoint, and the  
10 primary endpoint was not there. So I'm not reassured  
11 that they're always going in the same direction. And  
12 ACCORD is not the only trial where stroke goes in a  
13 different direction than the other components. So I  
14 think that's something that needs to be looked at  
15 further.

16           There's a concern about the trial design.  
17 Because there's the initial evaluation of 200 events,  
18 that could have an impact. I'll discuss that a little  
19 further. But the specific one that's related to this  
20 is the addition of a type one error.

21           Because there are two sets of outcomes in  
22 this trial, there's an outcome for benefit that looks

1 at MACE, and there's an outcome for safety that looks  
2 at MACE- plus, how do you handle that when you have two  
3 sets of outcomes in the same trial, in terms of the  
4 type one error? And that's one that's going to be  
5 potentially difficult to reconcile.

6           When you look at other clinically relevant  
7 markers, blood pressure, weight change and low density  
8 cholesterol levels, we tend to feel that weight change  
9 is of significant importance. I'll add one more  
10 comment, the weight change seen in this drug, I would  
11 be hard pressed to see if that would actually have an  
12 outcome measure.

13           We know from recent data, though we haven't  
14 seen the published data, the Look AHEAD study actually  
15 had significantly more weight loss in the diabetic  
16 population with no apparent primary outcome impact.  
17 That data is not published, that was just in a press  
18 release, so that was a much more -- that was a greater  
19 amount of weight loss, five percent, than you saw with  
20 this agent.

21           So I think this level of weight loss, it's  
22 better than gaining weight, but I don't think we can

1 make any long-term outcomes, or predictions of how  
2 that's useful.

3           In terms of blood pressure, in terms of blood  
4 pressure medications, all the blood pressure  
5 medications tend to be reviewed by the cardio renal  
6 panel. They have effects on lowering blood pressure  
7 tend to have outcomes that are beneficial. This is a  
8 very unique way of lowering blood pressure.

9           It's not really attacking a pathophysiology  
10 mechanism; it's really related to osmotic diuresis.  
11 And I'm not sure that just lowering blood pressure by  
12 one of these mechanisms that's not in the  
13 pathophysiology of hypertension will you see the long-  
14 term benefit.

15           For LDL cholesterol, and other markers that  
16 are related to that, it's going in the wrong direction  
17 of what we would like. We would like it to actually go  
18 in the opposite direction, or potentially be neutral.  
19 And we've seen this before in the class of  
20 rosiglitazone where there is also an increase in LDL  
21 that was relatively small but it was in the wrong  
22 direction.

1           And so I think long-term studies are going to  
2 really have to look at what that impact of that small  
3 elevation of LDL cholesterol, a slightly smaller  
4 elevation of LDL particle size, means in terms of the  
5 long-term outcomes.

6           Finally, there's these issues about the trial  
7 design. You know there's a competing interest here.  
8 There's the interest for patients that agents that are  
9 efficacious, and potentially that could be useful to  
10 them, are available to them in a reasonable time. And  
11 then there's the balance of safety to protect these  
12 same patients.

13           One way that's being addressed, and it's  
14 still under a lot of discussion with the FDA, is to do  
15 this two-step model within the same trial, to look at  
16 preliminary events for initial evaluation, and then  
17 look at later events in the trial to see if it's safer  
18 at the lower 1.3 estimate.

19           There's some questions about whether this is  
20 the right way of doing the trial approach, and  
21 questions about the integrity of the trial. Not  
22 questions of how it's being handled from the sponsor.

1 Of course, they're keeping it double-blind and doing  
2 everything else possible, but in terms of intention to  
3 treat analysis and other related matters.

4           The benefit though is potentially the drugs  
5 would get to market sooner. And, if you had to do two  
6 separate trials, you would have a much later starting  
7 point for the second cardiovascular trial, so you  
8 wouldn't get the data sooner after approval. Because  
9 this trial's ongoing, you should have the data much  
10 sooner after approval, if the drug is approved, to make  
11 a decision about the long-term cardiovascular safety.

12           And I just want to add one last comment  
13 related to what Dr. Capuzzi mentioned is because this  
14 is a osmotic mechanism, there may be other factors that  
15 are being impacted that weren't really addressed or  
16 thought about.

17           And the ones that I've spent some of my  
18 career studying, aldosterone and renin-angiotensin is,  
19 you know, this osmotic diuresis, we really don't know  
20 what it's having on the renin-angiotensin aldosterone  
21 system directly.

22           And we know, in the cholesterol-lowering

1 world, there have been several agents that have had a  
2 negative cardiovascular mortality impact and there's  
3 been postulation that this may be involved with  
4 alternations to the renin-angiotensin aldosterone  
5 system. So that might be something further to look at  
6 in these ongoing trials in terms of a safety signal.

7 Any additions or comments or -- Dr. Proschan?

8 DR. PROSCHAN: A couple of things. With  
9 regard to the 30-day analysis, one thing that I think,  
10 you know, should be made clear is that it's really  
11 difficult. The FDA did absolutely the right thing in  
12 trying to look at that and you know, statistics is as  
13 much an art as it is a science. And so you have to do  
14 these kinds of things. I think they did absolutely the  
15 right thing; it's just very hard to interpret.

16 The other thing, with regard to the interim  
17 analysis, I think that this would have been a huge  
18 issue if the FDA had said, if you want to you can use  
19 the interim analysis, if you don't want to use that,  
20 you don't have to use that; maybe you could wait  
21 another six months and use the data then.

22 Then there'd be a huge issue with the interim

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1 analysis because the results would be very biased if  
2 they could pick and choose, do we want to include this  
3 or not include this? But I don't think that was the  
4 case here. I think that was the plan all along to use  
5 those data. So I don't think that is as big an issue as  
6 if it happened the way I described.

7 DR. THOMAS: Any other corrections or  
8 additions? Okay. At this time, we're going to take a  
9 10 minute break. I will remind the panel members that  
10 there should be no discussion of the topic while you're  
11 on this break. And we will reconvene at 3:45.

12 (A recess was taken.)

13 DR. THOMAS: We're going to start with  
14 question four, which is the first of the two voting  
15 questions. We will be using an electronic voting  
16 system for this meeting. Once we begin the vote, the  
17 buttons will start flashing, and will continue to flash  
18 even after you've entered your vote.

19 Please press the button firmly that  
20 corresponds to your vote. If you're unsure of your  
21 vote, or you wish to change your vote, you may press  
22 the corresponding button until the vote is closed.

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1           After everyone has completed their vote, the  
2   vote will be locked in. The vote will be then  
3   displayed on the screen. Mr. Briggs will read the vote  
4   from the screen into the record.

5           Next, we will go around the room and each  
6   individual voted will state their name and their vote  
7   into the record. And you can also state a reason why  
8   you voted as you did, if you want to.

9           And I'd just add, and the FDA greatly  
10   appreciates the comment of why you voted, regardless of  
11   what your vote was. We will continue in the same  
12   manner until all questions have been answered or  
13   discussed.

14           I'm going to read question four. Dr. Gregg?  
15   Yes. If you can turn your mic on.

16           DR. GREGG: So to clarify, we have two  
17   separate voting questions?

18           DR. THOMAS: Yes, we have two separate voting  
19   questions. This one, which I'll read out. And then we  
20   have an additional voting question, question number  
21   five. Any other questions before I read question number  
22   four? Okay.

1           In accordance with FDA's guidance for  
2 industry titled, Diabetes Mellitus -- Evaluating CV  
3 Risk in New Anti-diabetic Therapies to Treat Type 2  
4 Diabetes, at the time of NDA submission, all applicants  
5 are to compare the incidence of important  
6 cardiovascular events occurring with their  
7 investigational agent to the incidence of the same  
8 types of events occurring with the control group, to  
9 show that the upper bound of the two-sided 95 percent  
10 confidence interval for the estimated risk ratio is  
11 less than 1.8.

12           Based on the data submitted, and considering  
13 the points of discussion in question three, do you have  
14 any concern regarding a conclusion that a risk margin  
15 of 1.8 has been excluded for canagliflozin? If you  
16 voted yes to question number four, remember to please  
17 provide your rationale when we go around the room. If  
18 you voted no to question number four, please provide  
19 your rationale. Dr. Brittain?

20           DR. BRITTAIN: Yeah, I just wanted to get a  
21 clarification because it seemed like this question is  
22 asked in a way that's kind of backwards to the way we

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1 usually ask, they ask. A is -- voting yes, means I  
2 have concerns; voting no, means I do not have concerns.  
3 Is that right? Okay.

4 DR. THOMAS: So voting, so just to clarify,  
5 so voting yes means you have concerns?

6 DR. PARKS: Let's just read the question. Do  
7 you have any concerns regarding a conclusion that risk  
8 margin 1.8 has been excluded for canagliflozin? Yes or  
9 no? Do you have any concern? Yes, I have concern.  
10 No, I do not have a concern. Does that help?

11 DR. THOMAS: Dr. Lewis, you had -- you just  
12 turned your mic on. You had a question? Can you turn  
13 your mic on?

14 DR. LEWIS: Does this question very narrowly  
15 address this whole issue of the proportionality thing,  
16 and yes, you buy that it's okay or it's not? Is that  
17 what this question is? And then which one of these, if  
18 you think that yeah, it all worked out, I believe what  
19 Dr. Brittain said about the proportionality thing is  
20 cool, then you would vote B? I'm just trying to -- I  
21 actually don't understand what I'm supposed to do.

22 DR. THOMAS: Dr. Kaul?

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1 DR. KAUL: I mean the way it is phrased, the  
2 answer is always going to be yes because any concern --  
3 all of us have some concern. So I mean I'd like to get  
4 a better understanding of -- a major concern.

5 DR. PARKS: Yes. I think that's where the  
6 rationale part will be very, very critical. I mean  
7 it's conceivable that you have heard all the  
8 discussions this morning, this afternoon, and you're  
9 convinced that, you know all the items that were  
10 discussed under point three have satisfactorily been  
11 addressed, conceivable that you have no concern.

12 But if you have any lingering, then I don't  
13 want to in any way bias your vote here, but if you have  
14 any lingering concern, you can say vote yes, and  
15 explain what that concern is. It may be a minor or a  
16 major concern. But I just want to make sure -- is that  
17 all right with you or do you want to make it more  
18 simple? Yes or no?

19 DR. LEWIS: Are you still just wanting us to  
20 address the narrow question of the 1.8 issue and  
21 proportionality? Because the next question seems to  
22 get more broad concerns. Or are you wanting to ask --

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1 are you trying to ask us, do we have any concerns about  
2 cardiovascular stuff?

3 DR. ROSEBRAUGH: Just a minute. So I think  
4 what we're trying to get at with this question is,  
5 unlike question five, which is decisional, this  
6 question is more just to help us get a sense of your  
7 comfort with the certainty of the cardiovascular data  
8 that we've been provided.

9 So I wouldn't view this, if you answer one  
10 way or the other, that's made the decision on whether  
11 the drug should be marketed, it's more to help us  
12 because we have been struggling with this 30-day issue  
13 and some of the other issues, so we just want to get a  
14 sense of how concerned you are about these issues. And  
15 I don't -- were you going to read your statement again,  
16 your opening statement? Was there something to help?

17 DR. GUETTIER: Yes, if I can reread the  
18 opening remarks I made this morning about this  
19 question. So for this question we want you to weigh  
20 the totality of the evidence surrounding cardiovascular  
21 safety, including the issues raised in discussion point  
22 three, so it's not just limited to the proportionality

1 hazard, to tell us whether you have concerns in  
2 concluding that a cardiovascular risk margin of 1.8 has  
3 truly been excluded for canagliflozin.

4           So again, it's the totality of the  
5 cardiovascular safety data. And it basically follows  
6 from the discussion points for question, for discussion  
7 point three, the bullet points for discussion point  
8 three.

9           DR. THOMAS: Dr. Proschan?

10           DR. PROSCHAN: So I take it from that, that  
11 you don't intend to change, to modify concerns to say  
12 serious concerns or -- you want it just as it is?

13           DR. ROSEBRAUGH: Yeah. And I think you can  
14 modify, in your response, when you answer us, whether  
15 you think it's serious or not.

16           DR. THOMAS: Okay. So I think the upshot is  
17 your discussion will be very helpful to the FDA. Okay,  
18 we'll go on then. If there's no further discussion on  
19 this question, we will not begin the voting process.

20           Please press the button on your microphone  
21 that corresponds to your vote. You have approximately  
22 20 seconds to vote. Please press the button firmly.

1 After you've made your selection, the light may  
2 continue to flash. If you're unsure of your vote, or  
3 you wish to change your vote, please press the  
4 corresponding button again. You can vote now.

5 DR. BRIGGS: The vote is eight yes, seven no,  
6 zero abstentions.

7 DR. THOMAS: We'll now go around the room.  
8 And just remember to state your name for the record,  
9 your vote and your rationale for your vote. And we'll  
10 start with, on my left, Dr. Hiatt.

11 DR. HIATT: Well yes, I do have residual  
12 concerns. In terms of taking that question literally,  
13 there's no doubt that the upper bound of 1.28, .29 is  
14 way below 1.8. Also, it's unlikely that that bound  
15 will get to 1.8 at the conclusion of the cardiovascular  
16 outcomes trial, but it could go above 1.3.

17 And so as -- not to dwell on sort of some  
18 earlier comments, but the idea that there's an early  
19 risk signal likely won't change, because the study's  
20 recruited. The probability of a late risk signal,  
21 because of the LDL effects, may be impactful.

22 But here's where I sort of wind up on this.

1 If this outcomes trial is run to completion, from 200  
2 events to 500 events, and the point estimate is still  
3 below 1.0, and the upper bound is still below 1.3, then  
4 I think that significantly mitigates this early risk  
5 concern. That's kind of -- I think that's sort of the  
6 thing that's most concerning, because that's in front  
7 of us, right.

8                   And so if that's still going to be there,  
9 which is likely going to be there, but overall, you see  
10 that these results that we currently are looking at,  
11 they just remain unchanged. And the point estimate is  
12 still less than 1.0 and the upper bound is less than  
13 1.3, then I think you can say to a patient, look you  
14 take this drug, there may be some imbalances early on,  
15 but overall you're going to be fine.

16                   And so therefore I think the answer to these  
17 lingering concerns is really in the totality of the  
18 data, which we don't have yet. And that's my lingering  
19 concern.

20                   DR. KNOWLER: Well I basically have no  
21 concern -  
22                   -

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1 DR. THOMAS: Dr. Knowler, if you could  
2 introduce yourself and your vote.

3 DR. KNOWLER: Yes, William Knowler. I voted  
4 yes, that I have a concern. I'm actually quite  
5 satisfied with the data that we have seen, that the  
6 drug is safe in terms of cardiovascular events. But as  
7 I stated in earlier discussions, I cannot have all my  
8 concerns allayed by data which, for the most part, only  
9 go for about a year, or some for a little bit longer.  
10 I think to be perfectly satisfied, I need to see longer  
11 term data, especially in view of the lipid risk  
12 factors.

13 DR. GREGG: I'm Ed Gregg. I voted yes. I  
14 actually do not have concern about the overall  
15 cardiovascular disease risk ratio here, and was not  
16 actually that concerned about the first 30 days as I  
17 saw that due to a reliability and probably due to  
18 chance.

19 Where I had some concern, to answer the  
20 question more directly, and particularly related to the  
21 1.8, was with stroke, because that was a more general,  
22 from a generalized analysis over the entire length. So

1   that would be where I would say some concern.

2                   DR. CAPUZZI:  Yes, I voted yes.  And --

3                   DR. THOMAS:  Dr. Capuzzi, if you could just  
4   state your name.

5                   DR. CAPUZZI:  Oh, I'm sorry.  David Capuzzi  
6   is my name.  Just a couple of points, part of the issue  
7   here has been this huge volume of material that just  
8   flows in incoherent, well not incoherent, but in a  
9   diffuse way.  It's very hard to follow the reasoning of  
10  it.

11                  However, I mentioned the lipid data, that's a  
12  concern.  I'm not sure it would be a reasonable concern  
13  if people knew ahead of it, prospectively while they  
14  were treating the patient and got everything in order.  
15  This is something that just popped up, and it wasn't  
16  explained well in the text.  But that is an issue.  
17  That is an issue.

18                  And you know, and that doesn't mean that --  
19  the other -- but one of the things that I'm concerned  
20  about is there are international companies running  
21  analogs of this and they're not part of the United  
22  States.  On the other hand I don't like to see that

1 happen because I don't know that there's the same care  
2 and follow up with people like that, and with other  
3 nations in other words.

4                   But, so I really have mixed feelings and I  
5 just hope that this could be straightened out. That's  
6 my really, my only rationale. And this was very  
7 diffusely written and hard to read. But the issue, as  
8 I understand it, and I still have some edginess because  
9 of the negativity shown in the results. And let's see,  
10 the next question, provide your rationale. Oh, I'm  
11 sorry.

12                  DR. THOMAS: Well we'll wait until the next  
13 question after the vote. Dr. Brittain?

14                  DR. BRITTAIN: Erica Brittain. I voted no.  
15 Of course I have at least some concerns, so I did not  
16 take the question literally. But I voted no, even  
17 though there are certainly some uncertainties about the  
18 cardiovascular risk with respect to the first 30 days,  
19 and certainly not much information about long-term  
20 follow up.

21                  But with respect to the prespecified 1.8  
22 benchmark, and that benchmark was, I assume,

1 established with the understanding that the data were  
2 going to be fairly short-term, I think the evidence is  
3 quite clear. That said, it's critical that the CANVAS  
4 trial be completed and in such a way that it will  
5 provide meaningful long-term data.

6 DR. THOMAS: Abraham Thomas. I voted no. I  
7 think overall the data that was presented actually  
8 support that they're well under the 1.8 threshold. And  
9 there's nothing that was really presented that would  
10 give me the ability to say we were -- something should  
11 be altered to the program or the study.

12 However, that doesn't mean that there aren't  
13 concerns. The three that I would bring up are, the  
14 most concerning for me is actually the stroke, because  
15 it's in the wrong direction and I'm not reassured the  
16 other factors, because they're going in the right  
17 direction, are enough to say it's safe. But there's no  
18 way of answering that question without more data, and  
19 so the rest of the trial is going to hopefully add to  
20 that and see if it's a real concern or not.

21 The LDL cholesterol one of course to me is  
22 also a concern, and that really also needs longer term

1 data than an interim analysis that was used here  
2 because you need probably several years to see that  
3 impact of LDL cholesterol.

4 And the last one, which I'm not too concerned  
5 right now, is the 30-day analysis, just because it's  
6 quite possible that's chance. However, that shouldn't  
7 be neglected in the future analysis and we'll see if  
8 that's a real factor or not. We may actually never get  
9 that answer, but at least hopefully with more data  
10 we'll be reassured.

11 DR. COOKE: David Cooke. I voted no.  
12 Placing the weight on the prespecified outcome,  
13 cardiovascular outcome that was well below 1.8, I'm  
14 comfortable that they showed that very easily. I think  
15 I agree that the post hoc analysis that identified the  
16 early cardiovascular events and the strokes is  
17 something to be considerate of, to think about. And  
18 certainly I would agree that the stroke outcome is of  
19 most interest, but that should come out with longer  
20 term data, but otherwise I'm comfortable with where we  
21 are now.

22 MS. KILLION: I'm Rebecca Killion and I voted

1 no. I'm not going to reiterate what's been better said  
2 by my other colleagues at the table, but I will now  
3 make a statement with at least five qualifying elements  
4 to it.

5           At this stage, and with the information that  
6 we have now available, I have no overriding concerns  
7 about the CV risk, but I think that the story continues  
8 to unfold, and more will be revealed as the study  
9 continues and we need to stay on top of that.

10           DR. KAUL: Sanjay Kaul. I voted no. I think  
11 the concerns that I have with regard to the  
12 cardiovascular database I've already enunciated. It  
13 was interesting to learn that the guidance, the FDA's  
14 guidance is a dynamic document. It's not a rule, it's  
15 only a guideline and it's interesting to see how it is  
16 evolving, or will evolve in the future with this  
17 precedent-setting drug.

18           The couple of things that I would like the  
19 sponsor to do is to sort of clarify, or better  
20 characterize the endpoints in order to understand what  
21 the clinical impact is on the patient. And I'm sure  
22 all the data is already available there, you just had

1 to go back and look at it, and maybe it would even be a  
2 post hoc adjudication of a Rankin score and see what  
3 the impact is.

4           What is the relevance of this unstable angina  
5 leading to hospitalization? Does that translate into  
6 something meaningful or is it just one of those soft  
7 endpoints that does nothing but add noise to it and  
8 sort of shift the upper bounds towards the null?

9           And this early hazard, it's difficult to make  
10 much of it. I'm not willing to completely dismiss it.  
11 I think the protocol needs to be amended, if it hasn't  
12 already been done, to capture the early events because  
13 the first patient visit was at six weeks, and the  
14 events cluster around day 30.

15           It's quite possible that you may have failed  
16 to capture some of the events, clinical or laboratory  
17 events, with all these events occurring beyond the  
18 first time period of assessment.

19           I have concerns about the fact that the  
20 dataset is only one year. I would like for a chronic  
21 disease --

22           DR. THOMAS: Dr. Kaul, sorry to interrupt

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1 you, but could you repeat what you said when you turned  
2 away from the microphone, or come close to it for the  
3 transcriptionist? Thank you.

4 DR. KAUL: Okay. I'm so sorry, I was  
5 addressing them. So my name is Sanjay Kaul. I voted  
6 no, but I do have concerns. The first concern I have  
7 is that the exposure, the period of exposure is rather  
8 limited. For a chronic disease, I would at least  
9 expect to see a longer follow up. And I think the --  
10 it's reassuring to know that the longer follow up will  
11 be coming.

12 I would like the sponsor to go back and  
13 better characterize the events, specifically whether  
14 the strokes were disabling or not. Characterize the  
15 type of MIs. Were they clinically uncertain biomarker  
16 elevation events, periprocedural events, or were they  
17 real spontaneous Q-wave myocardial infarctions?

18 I would also like them to sort of amend the  
19 protocol, if they haven't already done that, to assess  
20 the patients, the first visit earlier, in order to  
21 capture some of the early hazard, if it is real. And  
22 that's it.

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1 DR. COOK: Nakela Cook. And I voted yes.  
2 And I voted yes predominately because I still do have  
3 some concerns. And I think that they've been voiced  
4 here, and some concerns that people had the same ones  
5 and voted no for.

6 So I think the issue for me was really around  
7 stroke and whether or not that increased hazard is  
8 really real, and whether or not time would actually  
9 take that above the 1.8, in addition to the increased  
10 LDL levels.

11 And so kind of trying to figure out if longer  
12 follow up with those two issues would actually make me  
13 feel confident that we were at 1.8, and I didn't think  
14 so with my vote.

15 DR. PROSCHAN: I'm Michael Proschan and I  
16 voted no. I think, when you look at overall  
17 cardiovascular events, to me there's no question that  
18 they've shown that it's under 1.8.

19 With respect to, you know one component,  
20 namely stroke, I still have some questions about that.  
21 It's hard to feel confident that, you know that there's  
22 no increased risk given that confidence interval. But

1 for overall cardiovascular, I think they've  
2 demonstrated what they needed to.

3           And so, and I can't say whether this stroke  
4 thing is real or not. With regard to the 30-day  
5 events, I can't be sure that that's not real either,  
6 but I think it's -- I would -- I am betting that that  
7 is the play of chance.

8           DR. SAVAGE: I'm Peter Savage and I voted no,  
9 for many of the same reasons that have already been  
10 mentioned. I thought that in this case the, for  
11 overall cardiovascular disease risk, it looked to me as  
12 if they were very likely to have achieved the goal for  
13 meeting what the conditions were.

14           DR. MALARKEY: I'm Dave Malarkey and I voted  
15 yes. I was confident that the risk ratio of 1.8 wasn't  
16 met, but my biggest concern is the angst that's been  
17 shown by my fellow panelists who know more than I, and  
18 hearing that the data's not complete yet.

19           DR. LEWIS: Actually I'm not sure I can  
20 remember which is yes or no even now. But it sounds  
21 like we're all saying the same thing, whether we voted  
22 yes or no. But I actually am not worried about the

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1 first --

2 DR. THOMAS: Dr. Lewis, if you could just  
3 state your name and your vote.

4 DR. LEWIS: Oh, Julia Lewis. I'm not worried  
5 about the --

6 DR. THOMAS: And your vote.

7 DR. LEWIS: Oh, my vote was yes. So I wasn't  
8 -- I actually am not concerned about the MACE and the  
9 1.8 and the first 30 days or the stroke. I think, you  
10 know, I give them all that. I think the numbers,  
11 overall, look good. It's a composite. I'm okay with  
12 all that.

13 My residual concern remains that the number  
14 of people who have had sufficient follow up to assess  
15 the cardiovascular risk of LDL cholesterol being  
16 elevated, slightly worse renal function, higher  
17 phosphorus', I mean there are several things that could  
18 impact, and it might take longer. Even though a lot of  
19 people have gotten this drug, many of them it's for a  
20 very short time. So that was my residual concern.

21 DR. PALEVSKY: Paul Palevsky. I voted yes.  
22 I voted yes very narrowly based on the any in there, of

1 any concerns, same issues that I think everyone else  
2 has raised, particularly the stroke.

3 I suspect that that's not going to play out,  
4 but there's some concern there. I suspect that the 30-  
5 day data is a statistical aberration, but there is some  
6 concern there. So because of the word any, I voted  
7 yes.

8 DR. THOMAS: Dr. Rasmussen, would you want to  
9 comment on this or do you want to save your comments at  
10 the end of -- up to you.

11 DR. RASMUSSEN: I'll add a few comments here  
12 as it pertains to the CV risk assessment. The sponsor  
13 has conducted the largest program for a single compound  
14 in diabetes and collected 200 CV events, much more than  
15 we're used to seeing.

16 They've conducted the prespecified analysis  
17 according to the agreement they had with the agency,  
18 and came out with point estimates below 1.0 and with  
19 upper bounds less than 1.3.

20 The spirit of the guidance is to exclude an  
21 excess risk of 80 percent. So that's at least what's  
22 been discussed so far. And I think even though there

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1 are some lingering concerns, that we'll have an  
2 opportunity to address down the line with the accrual  
3 of more data. I think they've lived up to what they  
4 intended to do.

5 DR. THOMAS: Thank you. We'll now move on to  
6 a voting question, which is question number five. Dr.  
7 Lewis?

8 DR. LEWIS: I have a question about this  
9 question, which I guess I know the answer, but --

10 DR. THOMAS: Can I just have you wait until I  
11 read the question then I'm happy to take that.

12 DR. LEWIS: Yeah. Okay. Sorry.

13 DR. THOMAS: Okay. Based on the information  
14 included in the briefing materials and presentations  
15 today, has the applicant provided sufficient efficacy  
16 and safety data to support marketing of canagliflozin  
17 for the treatment of type 2 diabetes mellitus?

18 A, if you voted yes to question number five,  
19 please provide your rationale and whether you recommend  
20 any additional studies post-approval. B, if you voted  
21 no to question number five, please provide your  
22 rationale and discuss what additional data are

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1 necessary to potentially support approval. Dr. Lewis?

2 DR. LEWIS: The agency, and actually the  
3 sponsor, both gave us much information about the low  
4 GFR group. And I've already expressed my concern that  
5 it may not be in their best benefit risk issue to  
6 receive this drug.

7 This question does not allow -- if I vote  
8 yes, or if I vote -- yeah, if I vote yes, it goes to  
9 them as well. You didn't let us carve them out. Was  
10 that by intent or?

11 DR. PARKS: That was intentional. I think  
12 that if that is really a critical point for you. That  
13 may be a reason why you want to vote yes or no. And  
14 again, it goes to the rationale explaining why that  
15 should be.

16 DR. THOMAS: Dr. Knowler?

17 DR. KNOWLER: Yeah, I have a somewhat similar  
18 concern. I raised the question this morning about  
19 whether you were requesting approval to use the drug as  
20 an add-on to other medical therapy to diabetes, or as  
21 monotherapy, and again, this question doesn't address  
22 that.

1           But my own view, I might as well state it  
2 right now, is I see reasons to consider this as add-on  
3 therapy, but I see no reason to consider it as initial  
4 therapy when there have been no comparisons made with  
5 metformin, which is the standard initial therapy. So  
6 given that, I'm not quite sure how you would want me to  
7 vote.

8           DR. GUETTIER: So I think you know the  
9 indication for all anti-diabetic agent is a broad  
10 indication. A few years back we used to give  
11 indication as monotherapy, add-on to metformin therapy,  
12 and that has been done away. So we have a simplified  
13 indication for diabetes.

14           The results of all of the Phase III trials  
15 are in the label, under the clinical studies section.  
16 And although we don't specify anything, the data is  
17 there for physicians to look at.

18           DR. KNOWLER: So if I understand, you're  
19 saying the FDA now will not approve a drug for certain  
20 patients but not for others. It's either all or  
21 nothing?

22           DR. GUETTIER: The broad indication is

1 commensurate with the studies that were done in the  
2 Phase III program. So if the sponsor has studied  
3 different clinical scenarios, that will be in the  
4 label. If the sponsor has not studied other specific  
5 clinical scenarios, then there will be either a  
6 limitation of use in the label, saying that it's not  
7 appropriate for a specific clinical use scenario.

8           But if this particular sponsor has studied a  
9 monotherapy indication, the study for the monotherapy  
10 arm will be in the label, and physicians will be able  
11 to decide whether or not they want to use this as  
12 first-line therapy or as second-line therapy. But the  
13 FDA doesn't have any say in that.

14           DR. THOMAS: Is that enough, Dr. Knowler to  
15 vote?

16           DR. KNOWLER: Well I think you've answered my  
17 question, although I don't like the answer. I'm not  
18 sure what else we can do about it.

19           DR. PARKS: And I don't know if this is going  
20 to help you in determining how to vote, but if you  
21 think -- so what you're heard from Dr. Guettier here is  
22 that how the clinical development program has been

1 structured, the Phase III trials will be, if this  
2 product gets approved, will be described under the  
3 clinical studies section of the label, so that  
4 prescribers can be informed on the efficacy and safety  
5 in the many different uses of the anti-diabetic  
6 product.

7           Now, if you think that there is a method of  
8 use that has not been studied, and you think that it's  
9 a really critical method for use that you think that  
10 there's a large gap of knowledge there, then that might  
11 influence your decision.

12           If you think that there's a method of use  
13 that's missing, but not having it in the label, or as  
14 Dr. Guettier said, a limitations of use could still be  
15 helpful to the prescribing population where they can so  
16 oh, it hasn't been used here, I probably shouldn't use  
17 it, then that might also influence your vote. Does  
18 that help?

19           DR. THOMAS: If there's no further discussion  
20 on this question, we'll now begin the voting process.  
21 Please press the button on your microphone that  
22 corresponds to your vote. You have approximately 20

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1 seconds to vote. Please press the button firmly.

2           After you've made your selection, the light  
3 may continue to flash. If you're unsure of your vote,  
4 or you wish to change your vote, please press the  
5 corresponding button again.

6           DR. BRIGGS: The vote is 10 yes, five no,  
7 zero abstentions.

8           DR. THOMAS: We'll start around the room to  
9 my left. Dr. Hiatt? Just a reminder, please state  
10 your name and your vote and then your rationale on how  
11 you voted yes or no.

12           DR. HIATT: William Hiatt. I voted no. Just  
13 to be brief, I think the cardiovascular risks have not  
14 been fully evaluated. And I think that they will be,  
15 hopefully it sounds like maybe it will take two years.

16           Though the sponsor did show some updated  
17 numbers on those events that I didn't know how you got  
18 there, if you weren't continuing to unblind the  
19 outcomes trial. But I would hope that these issues,  
20 residual issues I have, would be resolved at the  
21 completion of the outcomes trial.

22           DR. KNOWLER: William Knowler. I voted no

1 for the reasons I just described a few minutes ago.  
2 Basically I think the drug would be acceptable as add-  
3 on therapy in some patients, but for a general  
4 indication, including monotherapy, I cannot recommend  
5 it.

6 DR. GREGG: I'm Ed Gregg. I voted no. The  
7 risk benefit judgments are unfortunately subjective,  
8 and this one was particularly difficult. I found that  
9 we saw a diverse set of benefits here, but they were  
10 largely surrogate outcomes wherein the mechanism this  
11 novel could conceivably affect the long-term impact.  
12 And I found this clouded by the fact that the benefits  
13 were less in a large segment of the target population.

14 And we had a variety of lingering questions,  
15 ranging from bones and fractures, to renal function, to  
16 stroke, volume depletion. And so in the end, I found  
17 myself weighing a lot of maybe benefits versus a lot of  
18 maybe risks. And I would have felt I think -- perhaps  
19 my uncertainty would have been diminished if we had a  
20 full sample for two years. So that would be my  
21 recommendation.

22 Aside from the fact that when you have a lot

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1 of -- a diverse set of benefits and risks like this, it  
2 would have been nice actually to see some data on  
3 function and quality of life and I didn't see that in  
4 the mix here.

5 DR. CAPUZZI: Yes, I voted no. It's not a  
6 negative no, it's a positive no. But at the same time,  
7 it's a tough decision and I think we're all thinking  
8 along the same lines. I just don't think there's  
9 enough data here. I think that it will come out just  
10 fine --

11 DR. THOMAS: Dr. Capuzzi?

12 DR. CAPUZZI: Yes?

13 DR. THOMAS: One, if you can state your name.  
14 And two, just --

15 DR. CAPUZZI: Well, my name, David Capuzzi.

16 DR. THOMAS: And just to make sure, you said  
17 you voted no but --

18 DR. CAPUZZI: I voted no and it's staying  
19 that way.

20 DR. THOMAS: No, no. You're listed as voting  
21 yes on the --

22 DR. CAPUZZI: Was it -- wait a minute, what

1 was the question? Oh, wait a minute. I'm sorry, wait  
2 a minute. Thanks a lot.

3 DR. THOMAS: While we do this. We'll come  
4 back to you while you're just clarifying if you need a  
5 moment to think about it. Dr. Brittain?

6 DR. BRITTAIN: Yeah, Erica Brittain. I voted  
7 yes. You know, I thought the efficacy results were  
8 very robust, even with some signs of superiority in the  
9 non- inferiority trials.

10 Yes, it is -- a primary endpoint is a  
11 surrogate endpoint, and that's not, you know obviously  
12 that has problems, but it was, again it was and agreed  
13 upon primary endpoint, and the results were very strong  
14 on that.

15 And it seemed, the results seemed strong  
16 enough to outweigh some lingering safety issues, the  
17 renal issues, the bone issues. And then there's this  
18 slightly confusing cardiovascular picture, but actually  
19 I think the cardiovascular picture's fairly promising,  
20 although as we said before, it will be very important  
21 to get the long-term data from the CANVAS trial.

22 I did also want to concur with others that

1 the risk benefit trade-off for the renal impaired  
2 population, however it gets defined, clearly is less  
3 clear cut.

4 DR. THOMAS: Abraham Thomas. I voted yes.  
5 There are definitely benefits to this drug. There are  
6 risks. I still have concerns, as many others do. One  
7 thing I'm reassured about is, you know MACE, the reason  
8 we use MACE is to accumulate enough events.

9 Each individual component, it's unlikely  
10 you'll enough events, so even with the issue of stroke,  
11 you may not see enough events during the trial to be  
12 able to make a final decision about safety or not.

13 But I'm reassured that in the past, in one of  
14 the over-the-counter obesity agents, the FDA was able  
15 to use epidemiologic and surveillance data to remove it  
16 from the market.

17 So I think one of the things that's important  
18 is in many of these areas, fractures, the  
19 cardiovascular risk, the long-term follow up should not  
20 be just the trial and specific trials addressing some  
21 of these issues, like bone safety, but really does have  
22 to involve registry data, surveillance data, HMO data

1 to pick up some of these factors that I think are  
2 really hard to identify in a trial no matter how large.

3 DR. COOKE: David Cooke. I voted yes. And  
4 again, I think the efficacy data were clear, at least  
5 in terms of the surrogate endpoint. I agree that  
6 ultimately a real outcome would be better.

7 But again, I think balancing the realistic  
8 expectations for investigations prior to approval,  
9 without putting excessive burden that would inhibit  
10 development and delivery of these medications to a very  
11 important needy population in terms of imperfect  
12 control currently.

13 And so although the risk data is incomplete  
14 at this point, I think it is sufficiently reassuring to  
15 justify the efficacy data and approval at this time.

16 MS. KILLION: I'm Rebecca Killion. I voted  
17 yes. I agree with everything Dr. Cooke just said. But  
18 as a patient, I have to say I found that this drug very  
19 encouraging from several points of view. One is, I  
20 think it particularly addresses concerns that patients  
21 have with respect to struggling with weight loss, which  
22 directly affects the progress of their disease, and the

1 concern that all diabetic patients have about  
2 hypoglycemia.

3           In addition, it improves the hemoglobin A1c,  
4 and it represents a step forward, progress, in that  
5 it's a new mechanism of action for a drug. So all of  
6 that's very encouraging from a patient perspective.

7           There are some concerns that I have. As I  
8 said previously, I think this story still is unfolding.  
9 But I think that, from a risk benefit analysis, every  
10 drug has risks and it's not appropriate for use in all  
11 populations, but I think that that will be able to be  
12 worked out. So from a patient point of view, this is  
13 very encouraging.

14           DR. KAUL: My name is Sanjay Kaul, and I  
15 voted yes, but with one caveat. I think the sponsor  
16 has shown that the benefit exceeds the risk in patients  
17 with normal or mildly impaired renal function. I do  
18 not believe that the benefit exceeds the risk in  
19 patients with moderately impaired renal function.

20           I think that patient population was  
21 underrepresented in this trial, and I think they need  
22 to enhance the evidence base, meaning do more trials

1 specifically enrolling patients at moderate risk,  
2 moderate renal impairment, because the hypoglycemic  
3 efficacy was significantly reduced in this patient  
4 population, and the adverse events were increased by  
5 two to four-fold.

6           Even though the ascertainment process was not  
7 prospectively prespecified, and it was not stringent,  
8 it may actually turn out to be worse. And so since  
9 half of the patients in the cardiovascular dataset have  
10 moderately impaired renal function that also applies to  
11 that dataset as well.

12           I have concerns about the cardiovascular  
13 assessment, which I've already enunciated prior. I  
14 think the FDA will have to ensure the issues regarding  
15 trial integrity. And that's it.

16           DR. COOK: Nakela Cook, and I voted no, and  
17 actually for similar reasons that Dr. Kaul just  
18 mentioned. I was concerned about the group with  
19 moderate renal impairment and not having the risk  
20 benefit ratio in the favor of benefit there outweighing  
21 risk.

22           I think that overrode my vote. I actually

1 even, though I had some concerns around cardiovascular  
2 risk, I felt like longer term follow up data would help  
3 us with that. I was more concerned about the moderate  
4 renal impairment group at this stage, with the data  
5 that we have currently.

6 DR. PROSCHAN: And I'm Michael Proschan. I  
7 voted yes. I felt like there was a lot of safety data,  
8 although you know it would be nice to have longer  
9 duration, five-year data for example. But I thought  
10 that there was substantially more safety data than in  
11 many diabetes drug trials.

12 I was also persuaded, obviously I'm not a  
13 clinician, but I was persuaded by the ones who said,  
14 you know who talked about the importance of having a  
15 new class that doesn't depend on insulin. And so I  
16 voted yes.

17 DR. SAVAGE: Peter Savage. I voted no. My  
18 main concern was also that the use in people with  
19 moderate renal disease might not be appropriate at this  
20 time with the data that's available. It seemed to me  
21 that the risk benefit ratio was different in that group  
22 and that I didn't feel comfortable, maybe because it's

1 not a field that I have as much expertise in, but I  
2 didn't feel comfortable that this wouldn't in some way  
3 actually damage the kidneys with long-term urinary  
4 tract infections and so forth.

5           So that I just felt that that tipped my vote  
6 from yes to no, because I think it could be useful in  
7 other parts of the diabetic population.

8           I guess there's two other brief things I'd  
9 like to mention. It was said that it would be useful  
10 in terms of avoiding the risk of hypoglycemia, but one  
11 thing that occurred to me, that wasn't mentioned at all  
12 today, is that amongst the elderly, the ability to  
13 recover from hypoglycemia is somewhat blunted.

14           And so they get sort of poorer glucagon  
15 responses and so forth, and therefore their glucose may  
16 come up more slowly. And if you've got something  
17 draining glucose out of the kidney at the same time, I  
18 don't know whether there's any extra danger of more  
19 prolonged hypoglycemia in older people. I think it's  
20 something that ought to be at least looked into.

21           And you know I agree also with Bill Knowler  
22 that it seems to me there was no evidence presented

1 here that would make me think that this would be a  
2 replacement for metformin unless you had someone who  
3 had a lot of GI symptoms that just couldn't take  
4 metformin.

5 But you know, that's not as much a -- that at  
6 least probably wouldn't be that harmful. But the  
7 kidney question I have concerns about.

8 DR. MALARKEY: I'm Dave Malarkey. I voted  
9 yes. I felt the benefits outweighed the risk in this  
10 situation. The relatively low risks in the animal  
11 studies were nicely done and supportive of mechanistic  
12 studies. I felt there's some uncertainty with the  
13 long- term effects that needs to be monitored closely.

14 DR. LEWIS: I'm Julia Lewis. I voted yes.  
15 And I guess my vote reflects the fact that I have great  
16 faith in my FDA colleagues. I know they listened to a  
17 long and I think a great discussion with my colleagues  
18 here at the table.

19 I would expect that the labeling would  
20 reflect our concerns in the low GFR group at the very  
21 least. And I would anticipate, and it sounds like you  
22 guys are really thinking about how to ensure that

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1 CANVAS does get completed with sufficient events in a  
2 timely time.

3           And the burden should be on the company to do  
4 that, and if not, they get cut off or something. I  
5 mean, then I bet you they'll find a way to do it.

6           So, but I am sure you will think of a way to  
7 make that happen. And with those two caveats, I felt  
8 comfortable that they had succeeded in fulfilling what  
9 was the intent and agreement with you, and was a  
10 reasonable approach to preliminary approval for this  
11 drug.

12           DR. PALEVSKY: Paul Palevsky. I voted yes.  
13 Similar concerns that I think have been expressed, both  
14 for the need for post-approval cardiovascular data, and  
15 with concerns about the use of the agent in the  
16 patients with more advanced kidney disease, the Stage  
17 3B, so eGFR of less than 45 group of patients.

18           DR. THOMAS: Dr. Capuzzi, if you want to read  
19 your name and your vote again, and your rationale?

20           DR. CAPUZZI: Yeah, could you just clarify,  
21 what was my first vote?

22           DR. THOMAS: Your -- you mean on question

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1 four?

2 DR. CAPUZZI: No, my question that was at --  
3 oh.

4 DR. THOMAS: The vote we just did was on  
5 question five, which was the approvability.

6 DR. CAPUZZI: Right.

7 DR. THOMAS: And you voted yes on that.

8 DR. CAPUZZI: Okay. All right. As I hear  
9 people, I'll leave it that way. But as I hear people  
10 that -- everybody has the same concerns and need for  
11 the sponsor to follow up with appropriate studies and  
12 safety issues. But I think it's a good opportunity,  
13 very good.

14 DR. THOMAS: And Dr. Rasmussen, even though  
15 you're not a voting member, if you have any final  
16 comments.

17 DR. RASMUSSEN: Just very briefly. I seem to  
18 say this every time, I mean this was not easy and I  
19 want to thank all of you for carefully deliberating  
20 both the benefits and the risks. The sponsor already  
21 has activities ongoing that hopefully will address  
22 these in a timely manner. So the agency has every

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1 opportunity to work with the sponsor to come up with a  
2 good solution.

3 DR. THOMAS: Do you have any final comments  
4 from the FDA?

5 DR. PARKS: Yes, I'd like to thank all the  
6 committee members, the chairman, Dr. Thomas, also Caleb  
7 for helping us out today. This has been a very dynamic  
8 and thoughtful discussion on some very difficult  
9 issues, and so we'll very much take all your rationale,  
10 your discussion points to heart.

11 I'd also like to thank the company for their  
12 presentations and working with us, especially in the  
13 last couple weeks, in responding to our requests. And  
14 then finally I'd like to thank the FDA review team for  
15 a phenomenal job preparing for this advisory committee.  
16 And particularly to Dr. Jean-Marc Guettier for leading  
17 up this multidisciplinary review team. Thank you.

18 DR. THOMAS: I'd like to thank the sponsor  
19 and the FDA for their excellent presentations, the  
20 panelists for their spirited discussion and excellent  
21 questions, the open public hearing speakers for their  
22 valuable input, and the audience for their attention.

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1 This meeting's adjourned. Thank you.

2 (Meeting adjourned at 4:36 p.m.)

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1 CERTIFICATE OF COURT REPORTER

2 I, NATALIA THOMAS, the Court Reporter before whom  
3 the foregoing proceeding was taken, do hereby certify  
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10 interest in this proceeding.

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