

1 FOOD AND DRUG ADMINISTRATION  
2 CENTER FOR DRUG EVALUATION AND RESEARCH  
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8 ENDOCRINOLOGIC AND METABOLIC DRUGS  
9 ADVISORY COMMITTEE (EMDAC) MEETING  
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12  
13 Thursday, December 12, 2013

14 8:00 a.m. to 4:45 p.m.  
15  
16  
17

18 FDA White Oak Campus  
19 Building 31, The Great Room (Room 1503)  
20 White Oak Conference Center  
21 Silver Spring, Maryland  
22

**Meeting Roster**

**DESIGNATED FEDERAL OFFICER (Non-Voting)**

**Karen Abraham-Burrell, PharmD**

Division of Advisory Committee and Consultant

Management

Office of Executive Programs, CDER, FDA

**ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY**

**COMMITTEE MEMBERS (Voting)**

**Erica H. Brittain, PhD**

Mathematical Statistician

Biostatistics Research Branch

National Institute of Allergy and Infectious

Diseases (NIAID)

National Institutes of Health (NIH)

Bethesda, Maryland

**William R. Hiatt, MD, FACP**

Professor of Medicine Division of Cardiology

University of Colorado School of Medicine

President, Colorado Prevention Center (CPC)

Clinical Research Aurora, Colorado

1     **Diana Hallare, MPH**

2     (Consumer Representative)

3     Visalia, California

4  
5     **Robert J. Smith, MD**

6     (Acting Chairperson)

7     Professor of Medicine (Endocrinology)

8     Alpert Medical School of Brown University

9     Ocean State Research Institute

10    Providence Veterans Administration Medical Center

11    Providence, Rhode Island

12  
13    **ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY**

14    **COMMITTEE MEMBER (Non-Voting)**

15    **Mads F. Rasmussen, MD, PhD**

16    (Industry Representative) Project Vice President

17    GLP-1 and Obesity - Global Development

18    Novo Nordisk A/S

19    Denmark

1       **TEMPORARY MEMBERS (Voting)**

2       **Barbara D. Berney**

3       *(Patient Representative)*

4       Amityville, New York

6       **Antonio Tito Fojo, MD, PhD**

7       Senior Investigator and Director Medical

8       Oncology Fellowship Program

9       Center for Cancer Research

10      National Cancer Institute, NIH

11      Bethesda Maryland

13      **Julia Lewis, MD**

14      Professor of Medicine

15      Vanderbilt University

16      Nashville, Tennessee

1     **Kevin D. McBryde, MD**

2     Program Director

3     National Institute of Diabetes, Digestive, and  
4     Kidney Diseases (NIDDKD)

5     Office of Minority Health Research

6     Coordination, NIH

7     Bethesda, Maryland

8  
9     **Milton Packer, MD**

10    Gayle and Paul Stoffel Distinguished Chair in  
11    Cardiology

12    Professor and Chair, Department of Clinical  
13    Sciences

14    University of Texas Southwestern Medical Center  
15    Dallas, Texas

16  
17    **Abraham Thomas, MD, MPH, FACP**

18    Division Head

19    Endocrinology, Diabetes, Bone & Mineral Disorders  
20    Whitehouse Chair in Endocrinology

21    Henry Ford Hospital

22    Detroit, Michigan

1     **Peter J. Savage, MD**

2     Senior Adviser for Clinical Research,  
3     Division of Diabetes, Endocrinology and Metabolism  
4     National Institute of Diabetes, Digestive, and  
5     Kidney Diseases  
6     National Institute of Health  
7     Bethesda, Maryland

8  
9     **Jürgen Venitz, MD, PhD**

10    Professor  
11    Department of Pharmaceutics  
12    Virginia Commonwealth University  
13    Richmond, Virginia

14  
15    **Miriam Vos, MD, MSPH**

16    Associate Professor of Pediatrics  
17    Division of Pediatric Gastroenterology,  
18    Hepatology and Nutrition  
19    Emory University School of Medicine  
20    Research Director, Health4Life Program  
21    Children's Healthcare of Atlanta  
22    Atlanta, Georgia

1     **Peter W. F. Wilson, MD**

2     Professor of Medicine

3     Emory University School of Medicine

4     Atlanta, Georgia

5  
6     **Wyndham Wilson, MD**

7     Senior Investigator and Deputy Branch Chief

8     Lymphoid Malignancy Branch

9     Center for Cancer Research

10    National Cancer Institute, NIH

11    Bethesda, Maryland

12  
13    **FDA PARTICIPANTS (Non-Voting)**

14    **Curtis Rosebraugh, MD**

15    Director

16    Office of Drug Evaluation II (ODE-II)

17    Office of New Drugs (OND), CDER, FDA

18  
19    **Jean-Marc Guettier, MD**

20    Director (Acting)

21    Division of Metabolism and Endocrinology Products

22    (DMEP), ODE-II, OND, CDER, FDA

1     **Frank Pucino, PharmD, MPH**

2     Clinical Reviewer

3     DMEP, ODE-II, CDER, FDA

4  
5     **Eugenio Andraca-Carrera, PhD**

6     Mathematical Statistician

7     Division of Biometrics VII

8     Office of Biostatistics

9     Office of Translational Sciences, CDER, FDA



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P R O C E E D I N G S

(8:00 a.m.)

**Call to Order**

**Introduction of Committee**

DR. SMITH: Good morning, everyone. If everyone could please take their seats, we can get started. I would like to remind everyone present to please silence your cell phones, BlackBerrys, and other devices, if you've not already done so. I would also like to identify the FDA press contact for this meeting, Morgan Liscinsky. If you're here, please stand.

My name is Robert Smith. I'm the acting chairperson for the Endocrinologic and Metabolic Drugs Advisory Committee. I will now call this meeting of the Endocrinologic and Metabolic Drugs Advisory Committee to order.

We'll start by going around the table and introducing ourselves. And let's start down on the right. We also have one member participating via telephone, and I'll ask him to introduce himself.

DR. RASMUSSEN: My name is Mads Rasmussen.

1 I work for Novo Nordisk, and I'm the industry  
2 representative on the panel.

3 DR. P. WILSON: Peter Wilson, Emory  
4 University, preventive cardiology, board-certified  
5 endocrinologist.

6 DR. PACKER: Milton Packer, University of  
7 Texas Southwestern, cardiologist.

8 DR. MCBRYDE: I'm Kevin McBryde. I'm a  
9 pediatric nephrologist, currently at the National  
10 Institutes of Diabetes and Digestive and Kidney  
11 Diseases, National Institutes of Health.

12 DR. LEWIS: Julie Lewis, nephrologist,  
13 Vanderbilt.

14 DR. FOJO: Tito Fojo, medical oncologist,  
15 National Cancer Institute.

16 MS. BERNEY: Barbara Berney. I'm your  
17 patient representative.

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

21 MS. HALLARE: Diana Hallare, consumer  
22 representative.

1 DR. SMITH: I'm Robert Smith. I'm professor  
2 of medicine and endocrinology at the medical school  
3 at Brown University.

4 DR. ABRAHAM-BURRELL: Karen Abraham-Burrell,  
5 designated federal officer.

6 DR. THOMAS: Abraham Thomas, division head,  
7 endocrinology, Henry Ford Hospital, Detroit,  
8 Michigan.

9 DR. SAVAGE: Peter Savage, endocrinologist  
10 at NIH at the National Institute of Diabetes and  
11 Digestive and Kidney Diseases.

12 DR. VOS: Miriam Vos. I'm a pediatric  
13 hepatologist from Emory University.

14 DR. W. WILSON: Wyndham Wilson, medical  
15 oncologist, National Cancer Institute.

16 DR. ANDRACA-CARRERA: Eugenio Andraca,  
17 statistician at the Food and Drug Administration.

18 DR. PUCINO: Frank Pucino, clinical  
19 reviewer, Food and Drug Administration.

20 DR. GUETTIER: Jean-Marc Guettier, acting  
21 director, Division of Metabolism and Endocrinology  
22 Products.

1 DR. ROSEBRAUGH: Curt Rosebraugh, director,  
2 Office of Drug Evaluation II.

3 DR. SMITH: Dr. Hiatt, could you also  
4 introduce yourself, please?

5 DR. HIATT: William Hiatt, division of  
6 cardiology, University of Colorado School of  
7 Medicine.

8 DR. SMITH: Thank you. For topics such as  
9 those being discussed at today's meeting, there are  
10 often a variety of opinions, some of which are  
11 quite strongly held. Our goal is that today's  
12 meeting will be a fair and open forum for  
13 discussion of these issues, and that individuals  
14 can express their views without interruption.  
15 Thus, as a gentle reminder, individuals will be  
16 allowed to speak into the record only if recognized  
17 by the chair. We look forward to a productive  
18 meeting.

19 In the spirit of the Federal Advisory  
20 Committee Act and the Government in the Sunshine  
21 Act, we ask that the advisory committee members  
22 take care that their conversations about the topic

1 at hand take place in the open forum of the  
2 meeting.

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

8 Also, the committee is reminded to please  
9 refrain from discussing the meeting topic during  
10 breaks or during lunch. Thank you.

11 We'll have the conflict of interest  
12 statement read by Karen Abraham-Burrell.

13 **Conflict of Interest Statement**

14 DR. ABRAHAM-BURRELL: Thank you. The Food  
15 and Drug Administration is convening today's  
16 meeting of the Endocrinologic and Metabolic Drugs  
17 Advisory Committee under the authority of the  
18 Federal Advisory Committee Act of 1972.

19 With the exception of the industry  
20 representative, all members and temporary voting  
21 members of the committee are special government  
22 employees or regular federal employees from other



1 agencies and are subject to federal conflict of  
2 interest laws and regulations.

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

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

19 Related to the discussions of today's  
20 meeting, members and temporary voting members of  
21 this committee have been screened for potential  
22 financial conflicts of interest of their own as

1 well as those imputed to them, including those of  
2 their spouses or minor children and, for purposes  
3 of 18 USC Section 208, their employers. These  
4 interests may include investments, consulting,  
5 expert witness testimony, contracts, grants,  
6 CRADAs, teaching, speaking, writing, patents and  
7 royalties, and primary employment.

8 Today's agenda involves the discussion of  
9 efficacy and safety of new drug application 202293,  
10 dapagliflozin tablet, submitted by Bristol-Myers  
11 Squibb. Dapagliflozin is a sodium-glucose  
12 co-transporter 2 inhibitor developed as an adjunct  
13 to diet and exercise to improve glycemic control in  
14 adults with type 2 diabetes mellitus.

15 This is a particular matters meeting, during  
16 which specific matters related to dapagliflozin  
17 will be discussed.

18 Based on the agenda for today's meeting and  
19 all financial interests reported by the committee's  
20 members and temporary voting members, conflict of  
21 interest waivers have been issued in connection  
22 with this meeting. To ensure transparency, we

1 encourage all standing committee members and  
2 temporary voting members to disclose any public  
3 statements that they may have made concerning the  
4 products at issue.

5 With respect to FDA's invited industry  
6 representative, we would like to disclose that  
7 Dr. Mads Rasmussen is participating in this meeting  
8 as a nonvoting industry representative, acting on  
9 behalf of regulated industry. Dr. Rasmussen's role  
10 at this meeting is to represent industry in general  
11 and not any particular company. Dr. Rasmussen is  
12 employed by Novo Nordisk.

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

21 FDA encourages all participants to advise  
22 the committee of any financial relationships that

1       they may have with the firms at issue. Thank you.

2               DR. SMITH: We'll now proceed with the FDA  
3       opening remarks from Dr. Guettier.

4               **FDA Introductory Remarks - Jean-Marc Guettier**

5               DR. GUETTIER: Good morning. My name is  
6       Jean-Marc Guettier, and I'm the acting director for  
7       the Division of Metabolism and Endocrinology  
8       Products at the FDA. I want to start by welcoming  
9       you all to this advisory committee meeting today.  
10       And I would also like to take this opportunity to  
11       thank Dr. Smith and the panel members for their  
12       presence.

13               The advisory committee was convened to  
14       discuss the new drug application for dapagliflozin.  
15       The dapagliflozin application has already been  
16       reviewed once, and to provide context and shed  
17       light on why specific topics of discussion were  
18       selected, I would like to focus my introductory  
19       remarks on the following three objectives.

20               I'll begin by briefly summarizing key  
21       aspects of the first review cycle. This slide  
22       graphically depicts the timeline for the first

1 cycle of review, beginning with application filing  
2 in December 2010 and ending with the decision to  
3 not approve dapagliflozin in January 2012.

4 I want to bring people's attention to the  
5 two other key dates depicted on this timeline.  
6 These are the July 2011 advisory committee meeting,  
7 and the submission of additional data to the  
8 application in November 2011, which constituted  
9 what we call a major amendment to the application.

10 In July 2011, an advisory committee meeting  
11 was held to discuss the dapagliflozin application.  
12 At the July 2011 advisory committee meeting,  
13 longer-term safety data was available from 14 phase  
14 2b/3 trials. The safety data was based on  
15 approximately 4300 cumulative patient-years of  
16 exposure to dapagliflozin and 1900 patient-years of  
17 exposure to comparators.

18 At the advisory committee meeting, efficacy  
19 and safety findings in the overall program were  
20 reviewed. In addition, specific emphasis was  
21 placed on particularly challenging aspects of the  
22 application.

1           These aspects were the efficacy findings in  
2 patients with moderate to severe renal impairment,  
3 liver safety findings, the finding of a breast  
4 cancer imbalance in female participants, and the  
5 finding of a bladder cancer imbalance in male  
6 patients.

7           The advisors were asked to opine on whether  
8 the efficacy and safety data in the dapagliflozin  
9 program supported approval of the product. The  
10 advisors expressed unease with regard to the large  
11 uncertainty around some of the identified risks,  
12 specifically for risks related to cancer and  
13 hepatotoxicity. Based on the data presented in  
14 July 2011, the majority of the advisors voted  
15 against approval.

16           During the first review cycle, additional  
17 data related to efficacy and safety of  
18 dapagliflozin were being collected from either  
19 extensions of parent trials included in the  
20 application or from trials started after initial  
21 database lock.

22           To assess the impact of additional exposure

1 on malignancy and liver safety risks, the FDA asked  
2 for updated analyses for these two serious  
3 identified risks. The FDA was also interested in  
4 receiving an updated estimate of cardiovascular  
5 risk. The reasons for this will be explained on a  
6 later slide.

7 In November 2011, longer-term safety data  
8 was available from now 19 phase 2b/3 trials. These  
9 data represented a 32 percent increase in  
10 dapagliflozin exposure compared to the original  
11 safety database and a 67 percent increase in  
12 exposure for comparators.

13 This slide summarizes the impact of  
14 additional exposure on the malignancy signal. The  
15 data in the table quantifies the strength of the  
16 association between exposure to dapagliflozin and  
17 the two malignancies identified as a safety signal.

18 The column on the left shows data presented  
19 at the July 2011 advisory committee meeting, and  
20 the column on the right shows the results for the  
21 updated analyses received in the November 2011  
22 major amendment.

1           The incidence rate of bladder cancer  
2       observed in males exposed to dapagliflozin relative  
3       to those exposed to comparators is shown in the  
4       first row. The point estimate shows that the  
5       incidence rate of bladder cancer was approximately  
6       five times more elevated in male subjects exposed  
7       to dapagliflozin than in subjects exposed to  
8       comparators, and that additional exposure did not  
9       appreciably change the strength of the association.

10           The incidence rate of breast cancer observed  
11       in females exposed to dapagliflozin relative to  
12       those exposed to comparator is shown in the second  
13       row. At the July 2011 advisory committee meeting,  
14       the incidence rate of breast cancer was  
15       approximately four times more elevated in females  
16       exposed to dapagliflozin than those exposed to  
17       comparators. With additional exposure, the  
18       strength of the association weakened.

19           This slide briefly summarizes key aspects of  
20       the liver safety finding from the first cycle of  
21       review. Categorical analyses comparing the number  
22       of individuals who experienced ALT elevation above



1       several specific thresholds did not reveal a  
2       between-group imbalance in marked alanine  
3       aminotransferase elevation in either the original  
4       or the updated data sets.

5               Please turn your attention to the table.  
6       Again, the left column refers to data presented at  
7       the 2011 advisory committee meeting and the right  
8       column to data received in the November 2011 major  
9       amendment.

10              The first row of the table shows the  
11       cumulative number of cases exposed to dapagliflozin  
12       who underwent a drug-related causality assessment  
13       by FDA hepatologists. These cases were  
14       specifically selected on the basis of marked  
15       elevation in alanine aminotransferase, accompanied  
16       by a concomitant rise in total bilirubin.

17              In a single case, the FDA hepatologist  
18       estimated that there was a 50 to 75 percent  
19       likelihood that the liver injury noted resulted  
20       from dapagliflozin use. This case occurred a 78-  
21       year-old man, and the features concerning for drug-  
22       induced liver injury are described here.

1           First, the patient experienced significant  
2   hepatocellular injury, as indicated by a PKLT rise  
3   above 1800. Liver injury was accompanied by liver  
4   function abnormalities, as indicated by the  
5   elevated total bilirubin level.

6           Second, the temporal pattern of  
7   hepatocellular injury was consistent with a pattern  
8   expected for a drug-related cause, with mild ALT  
9   abnormalities first, appearing within 3 months of  
10   exposure to dapagliflozin, and rising further with  
11   additional exposure.

12           Third, possible other etiologies consistent  
13   with this pattern of liver injury had been  
14   excluded.

15           Fourth, the biopsy results showing severe  
16   recent inflammation were interpreted as being  
17   consistent with a drug-related etiology.

18           Fifth, improvement was initially noted with  
19   de-challenge and only later with corticosteroid  
20   administration. Although some features of the  
21   biopsy results could have been consistent with  
22   autoimmune hepatitis, these features were

1 nonspecific and not thought to be pathognomonic for  
2 this etiology. In light of negative serology  
3 results for marker of autoimmune hepatitis and an  
4 age of onset not typical for this condition, this  
5 was not felt to be the most probable diagnosis.

6 During the review, the question arose as to  
7 whether data in the NDA was supportive of the  
8 notion that dapagliflozin conferred a unique  
9 benefit that would justify approval of the NDA in  
10 spite of the serious identified risks.

11 The applicant, advisors, and some FDA  
12 reviewers had pointed to preliminary data that  
13 suggested dapagliflozin could confer a unique  
14 cardiovascular risk profile. These data were the  
15 observation that dapagliflozin exerted an effect on  
16 several cardiovascular risk markers, listed here,  
17 and that the estimated hazard ratio of  
18 cardiovascular risk in the prespecified meta-  
19 analysis leaned in favor of dapagliflozin.

20 Knowing that a large amount of  
21 cardiovascular data had been accumulated since  
22 filing, the FDA asked the sponsor to update the

1 estimate of cardiovascular risk with the additional  
2 data on hand.

3 The data in the table summarizes the results  
4 of the cardiovascular risk assessments for the  
5 prespecified meta-analysis of 14 trials, shown in  
6 the left-hand column, and the cardiovascular  
7 analyses performed with the updated cumulative data  
8 from 19 trials, shown in the right-hand column.

9 In the prespecified meta-analysis, the  
10 estimated hazard ratio for the time to first  
11 occurrence of the four-component composite  
12 endpoint, MACE-plus, was 0.67.

13 The point estimate is at least suggestive  
14 that patients exposed to dapagliflozin had lower  
15 cardiovascular risk compared to subjects exposed to  
16 comparators. With accumulation of additional  
17 cardiovascular safety data, the estimate of risk  
18 was seen moving closer towards unity, suggesting no  
19 risk difference.

20 The FDA was particularly interested in the  
21 estimates of cardiovascular risk in a subgroup of  
22 trials from the updated November 2011 meta-

1 analysis. The subgroup was made up of two trials,  
2 which were not included in the prespecified meta-  
3 analysis and will be referred from here on in as  
4 trials 18 and 19.

5 The reasons FDA paid particular attention to  
6 this subgroup are listed here. First, these two  
7 trials were very similar in design.

8 Second, these two trials were the largest  
9 and longest trials of the 19 trials.

10 Third, these two trials together contributed  
11 more than 40 percent of the events in the updated  
12 analysis.

13 Fourth and most importantly, the patient  
14 population was viewed as particularly useful to  
15 inform cardiovascular risk. All patients in these  
16 trials had documented, established cardiovascular  
17 disease at baseline.

18 The patient population was enriched for  
19 comorbid conditions highly prevalent in the  
20 diabetes population, including dyslipidemia, renal  
21 dysfunction, hypertension, and obesity. And  
22 finally, the patient population was older and had

1 longer-standing diabetes compared to the other  
2 trials.

3 This slide summarizes the November 2011  
4 cardiovascular risk assessment by subgroups. The  
5 left-hand column shows the estimate of  
6 cardiovascular risk for the subgroup of trials  
7 whose patient population was not specifically  
8 selected for cardiovascular disease at baseline.

9 The right-hand column shows the estimate of  
10 cardiovascular risk for trials 18 and 19, where  
11 participant eligibility depended on having  
12 established and documented cardiovascular disease  
13 at baseline.

14 Results for the four-component composite  
15 endpoint, MACE-plus, are shown in the first row,  
16 and for the three-component MACE endpoint in the  
17 second row. Results from the subgroup of trials 18  
18 and 19, representing the largest and longest trials  
19 and enrolling patients at high baseline  
20 cardiovascular risk, were not consistent with the  
21 previously-held notion that dapagliflozin offered a  
22 unique cardiovascular risk profile.

1           In reaching a decision not to approve  
2       dapagliflozin in 2012, the FDA considered the  
3       following.

4           First, dapagliflozin's glucose-lowering  
5       mechanism was novel, a benefit.

6           Second, the applicant had convincingly  
7       demonstrated that use of dapagliflozin was  
8       associated with improved glycemic control at  
9       6 months and 1 year across multiple, relevant  
10      clinical use scenarios. However, the data in the  
11      NDA did not demonstrate a glycemic benefit of  
12      dapagliflozin use in patients with moderate renal  
13      impairment.

14          From the 2005 to 2010 NHANES data, it is  
15      estimated that approximately 20 percent of patients  
16      with diabetes in the U.S. have renal function at or  
17      below this range. Thus, the glucose-lowering  
18      benefit would not extend to a large segment of the  
19      diabetes population.

20          Finally, although the observed effect of  
21      dapagliflozin on several CV risk markers would  
22      perhaps predict a unique macrovascular disease

1 benefit of this product, preliminary data from a  
2 patient population enriched for cardiovascular  
3 disease were not supportive of this notion.

4 With regards to risk, the FDA could not  
5 ignore the strength of the association between  
6 malignancy and dapagliflozin use identified in the  
7 safety database. And finally, the one case of  
8 probable daily casts uncertainty with regards to  
9 the hepatic safety of the product.

10 In January 2012, the FDA issued a complete  
11 response letter. In the complete response issued,  
12 the applicant was asked to provide additional  
13 exposure data, with a minimum 52 weeks of data for  
14 trials 18 and 19, and to update analyses related to  
15 bladder cancer, liver safety, and cardiovascular  
16 risk. The sponsor was also asked to continue plans  
17 to perform a cardiovascular outcomes trial.

18 This slide summarizes key events of this  
19 application since the complete response letter. In  
20 July 2012, the applicant filed a dispute resolution  
21 request appealing the complete response action. In  
22 September 2012, the dispute appeal was denied.



1           In response to the dispute request, the path  
2 forward outlined in the complete response letter  
3 was upheld. The response also called for convening  
4 a second advisory committee meeting to discuss  
5 updated data on liver, breast, bladder, and  
6 cardiovascular risk.

7           Finally, in the response, the applicant was  
8 asked to provide a preclinical toxicology study to  
9 address the issue of bladder tumor promotion.  
10 Specifically, the applicant was asked to use a  
11 model that reflects human experience and addresses  
12 whether changes in urinary composition caused by  
13 dapagliflozin use can result in bladder tumor  
14 promotion.

15           This brings us to today's meeting. The  
16 applicant filed the dapagliflozin application for a  
17 second time in July 2013, and today the applicant  
18 and the FDA will present updates to the liver  
19 toxicity risk, breast cancer risk, bladder cancer  
20 risk, and cardiovascular risk. The committee will  
21 be asked to weigh in on the following issues.

22           Question 1 relates to cardiovascular risk.

1 I'm not going to read these questions. In essence,  
2 what we are asking relates to the two trials that  
3 were discussed in the introductory statements,  
4 trials 18 and 19, and how they should inform  
5 cardiovascular risk.

6 Question 2 deals with the malignancy signal  
7 identified in the application. Based on the  
8 information provided in the briefing package and  
9 the presentation at today's meeting, you should  
10 discuss your level of concern with regards to the  
11 observed association between dapagliflozin use and  
12 occurrence of cancer identified in this  
13 application.

14 You're going to hear a lot of different ways  
15 to analyze the cancer-specific data, and in your  
16 answer, we'd like you to be specific about what you  
17 think is or is not concerning to you.

18 Finally, you're going to hear an update on  
19 the liver toxicity signal in this program with the  
20 updated analysis. And we'd like to hear your level  
21 of concern with this toxicity.

22 I'm going to go on to question 5 first

1       because it's the most simple question to explain.  
2       This is actually an approvability question, and in  
3       your answers to the question, you should explain  
4       your rationale for why you think the drug should be  
5       approved or not approved.

6               Question 4 can be an approvability question  
7       or it doesn't have to be. As you know, in 2008 the  
8       FDA asked the sponsor to estimate cardiovascular  
9       risk with a certain level of precision premarketing  
10      and additional precision postmarketing. This is  
11      spelled out in the cardiovascular risk guidance.

12             Based on the data you hear today, we'd  
13      like you to opine on whether or not you think the  
14      applicant has provided sufficient evidence that  
15      dapagliflozin relative to comparators has an  
16      acceptable cardiovascular risk profile.

17             DR. SMITH: Thank you. We'll now proceed  
18      with the sponsor presentations.

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

1 advisory committee meeting, FDA believes that it is  
2 important to understand the context of an  
3 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  
7 financial relationships that they may have with the  
8 firm at issue, such as consulting fees, travel  
9 expenses, honoraria, and interests in the sponsor,  
10 including equity interests and those based upon the  
11 outcome of this meeting.

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

19 **Sponsor Presentation - Amy Jennings**

20 DR. JENNINGS: Thank you, Mr. Chairman.

21 Good morning, ladies and gentlemen of the  
22 FDA, members of the committee, and guests. I'm Amy

1 Jennings, the U.S. regulatory lead for  
2 dapagliflozin at Bristol-Myers Squibb.

3 Bristol-Myers Squibb and AstraZeneca are  
4 pleased to be here today to present data  
5 demonstrating that dapagliflozin is an important  
6 and needed treatment option for patients with type  
7 2 diabetes.

8 Dapagliflozin, or dapa, as we'll refer to  
9 today, is a highly selective inhibitor of the  
10 sodium glucose co-transporter number 2, which is  
11 the transporter responsible for the majority of  
12 renal glucose reabsorption.

13 Our proposed indication is for the use as an  
14 adjunct therapy to diet and exercise to improve  
15 glycemic control in patients with type 2 diabetes  
16 when used as either a monotherapy or when used in  
17 combination with other antidiabetic agents,  
18 including initial combination therapy with  
19 metformin or insulin.

20 Based on its mechanism of action,  
21 dapagliflozin is not recommended to be initiated in  
22 patients with moderate renal impairment, as defined

1 by estimated GFR less than 60.

2 Beginning in 2010, in December of 2010,  
3 Bristol-Myers Squibb and AstraZeneca submitted new  
4 drug applications for dapa. Dapa is currently  
5 approved in 38 countries, including the European  
6 Union and Australia, and we continue to work with  
7 the FDA to make dapa available to patients in the  
8 United States.

9 As you may recall, we first presented dapa  
10 before this committee in July of 2011. Questions  
11 were raised at that meeting with regard to dapa's  
12 potential to cause liver injury, and the numeric  
13 imbalances in bladder and breast cancer events.

14 Subsequent to that meeting, we submitted  
15 additional data along with updated analyses for  
16 liver, CV safety, and overall malignancies. The  
17 latter showed an improvement in the breast cancer  
18 profile. The agency then issued a complete  
19 response letter in January of 2012.

20 In communications with the FDA, including  
21 seeking dispute resolution, a path forward was  
22 established for us to resubmit the dapa NDA, which

1       was then resubmitted in July of this year.

2               The CRL and the subsequent NDA resubmission  
3       focus on three topics -- the question of hepatic  
4       safety, the numeric imbalance in bladder cancer  
5       events, and a request for an updated CV  
6       meta-analysis.

7               The additional data in the NDA resubmission  
8       provided a greater than 50 percent increase in  
9       patient-years exposure as compared to the initial  
10      NDA, or 40 percent if you're comparing to the  
11      4-month safety update. These data offer greater  
12      precision with regard to these three questions.

13              First, we have gained a better understanding  
14      of the one clinical case of concern for drug-  
15      induced liver injury. This new information makes  
16      this case not likely to be drug-related.

17              Second, while there is still an imbalance in  
18      events, the weight of evidence argues against a  
19      causal relationship to bladder malignancy.

20              Third, we continue to observe a favorable CV  
21      point estimate overall, and the data show no  
22      unacceptable increase in CV risk.

1           Considering these additional data along with  
2           the previously submitted data, we conclude that  
3           dapa has a favorable benefit/risk profile and would  
4           be an important additional to the physician's  
5           armamentarium.

6           Dapa's mechanism of action allows it to be  
7           added to other antidiabetic agents at any stage of  
8           the diabetes continuum provided the patient has  
9           adequate renal function. And the data we'll share  
10          today illustrate that dapa, through a comprehensive  
11          clinical program with more than 11,000 patients,  
12          provides clinically hemoglobin A1c reductions  
13          equivalent to metformin and glipizide, while also  
14          providing the added benefits of weight loss, blood  
15          pressure reduction, and a low intrinsic risk for  
16          hypoglycemia.

17          In our presentations today, Dr. Harold Bays  
18          of the Louisville Metabolic and Atherosclerosis  
19          Research Center will begin with a brief overview of  
20          the need for new therapies for patients with type 2  
21          diabetes.

22          Dr. Jim List will then provide an overview



1 of the dapa development program, which will be  
2 followed by Dr. Shamik Parikh and Dr. List then  
3 reviewing the efficacy and safety data of dapa,  
4 respectively.

5 The majority of our talk, however, will  
6 focus on the topics raised by the agency.  
7 Specifically, Dr. List will provide a more detailed  
8 look at our new data as relates to liver, CV  
9 safety, and overall malignancies. And Dr. Dean  
10 Bajorin from the Memorial Sloan-Kettering Cancer  
11 Center will provide his expert assessment of the  
12 bladder cancer cases observed in the clinical  
13 program.

14 To conclude our talk, Dr. John Wilding, a  
15 professor of medicine from the University of  
16 Liverpool and a practicing diabetologist from the  
17 U.K., will translate the benefits and risks of data  
18 into the clinical practice. And Dr. List will  
19 share our commitment to continue to assess these  
20 characteristics of dapa in the post-approval  
21 setting.

22 In addition to our presenters, we have

1 several other experts with us to help answer your  
2 questions.

3 I'd now like to invite Dr. Bays to discuss  
4 the need for new therapies for patients with type 2  
5 diabetes.

6 **Sponsor Presentation - Harold Bays**

7 DR. BAYS: Thank you, Amy, and thank you all  
8 for being here. My name is Harold Bays. I'm a  
9 paid consultant. My institution has received  
10 research funding for some of our clinical trials,  
11 and I have no financial relationship that is  
12 dependent upon the outcome of this committee  
13 meeting.

14 What I'm here to talk about is the unmet  
15 needs in diabetes mellitus. Again, my name is  
16 Harold Bays, the medical director of a research  
17 facility located in Louisville, Kentucky.

18 So the first thing I want to talk about is I  
19 want to talk about the costs of the diabetes  
20 mellitus. I think we're all aware of the monetary  
21 costs, the huge monetary costs, of diabetes  
22 mellitus. But I want to focus on the patient.

1           With regard to the patient, in the United  
2       States about 8.3 percent of adults have diabetes  
3       mellitus. But even more concerning is the  
4       potential future, in that 35 percent over 20 years  
5       of age have pre-diabetes.

6           If you look at it from an adverse experience  
7       standpoint, for every 24 hours there are 4,000 new  
8       cases of diabetes mellitus, 810 deaths, 230  
9       amputations, 120 kidney failures, 55 cases of  
10      blindness. So clearly this can be devastating  
11      complications to those patients who experience  
12      these morbid conditions.

13          So how are we doing? What can we do to  
14      improve the outcome of our patients? Well, one of  
15      the things that we can do is we can improve glucose  
16      levels. And that is the reason you do have these  
17      treatment targets that have been established by  
18      scientific organizations, and you can see here on  
19      this slide that there's very different levels. But  
20      the essential message here is that not everyone is  
21      able to achieve the hemoglobin A1c goals as  
22      determined by these scientific organizations. And

1       therefore, there is this unmet need.

2               Why do we want to get the patients under  
3       control? Well, there's a dispute as to whether or  
4       not reduction in glucose levels can reduce  
5       cardiovascular disease, and I'm really not going to  
6       get into that. But where I think there is a  
7       general consensus is that improvement in glucose  
8       levels in patients with diabetes mellitus can  
9       improve microvascular disease.

10              Now, when we talk about microvascular  
11       disease, what we're talking about is nephropathy,  
12       diabetic kidney disease, or retinopathy, diabetic  
13       eye disease, or neuropathy, which is a nerve  
14       disease associated with the diabetes mellitus.

15              When it comes to cardiovascular effects of  
16       pharmaceutical interventions, I think you have to  
17       look at the totality of the effects of the  
18       pharmacological agent. And what are the types of  
19       things you might focus on?

20              Well, you might focus on what are the  
21       effects upon body fat. What are the effects upon  
22       blood pressure? Glucose? Lipids? Other factors?

1       So it is not just one isolated effect of a  
2       particular pharmaceutical that should be focused  
3       upon because the net cardiovascular effects of a  
4       pharmacological intervention is not always  
5       predictable and often dependent upon multiple  
6       metabolic considerations.

7               Another thing that we've learned is, yes,  
8       nobody's more passionate than I in believing that  
9       adipose tissue is a pathogenic organ. You have  
10      this pathos of adipose tissue, what we call  
11      adiposopathy, this pathos of adipose tissue. But  
12      what we've also learned is no matter the metabolic  
13      response or immune response or pre-fatty acid  
14      response, it very much matters the crosstalk and  
15      the interaction with other body organs.

16             Traditionally, we focused on things like the  
17      liver and the muscle and the pancreas. But we've  
18      come to understand now that the kidney also plays  
19      an important role in glucose regulation.

20             When it comes to pharmacological therapy and  
21      you're trying to speak to cardiovascular events,  
22      one meta-analysis has this quote. And this is,

1       again, my opinion. I agree with this quote, that  
2       overall, intensive compared with standard glycemic  
3       control significantly reduces coronary heart events  
4       without an increased risk of death.

5               However, the optimal mechanism, speed, and  
6       extent of hemoglobin A reduction may be different  
7       in differing populations. In other words, for many  
8       anti-diabetes mellitus agents with regard to  
9       coronary heart disease, it isn't just that you  
10      lower the glucose levels. It's how you lower the  
11      glucose levels.

12             So when you look at the totality of the  
13      patient -- now, you want to get back to the  
14      patient -- the totality of the patient, when you  
15      look at a patient with diabetes mellitus, what you  
16      want to target and treat are multiple metabolic  
17      parameters.

18             So you want to focus on the body weight.  
19      You want to focus on the lipids. You want to focus  
20      on the blood pressure. You want to focus on the  
21      glucose levels, physical activity, smoking  
22      cessation, all of these things. It's the totality

1 of the pharmacological agent.

2 Well, we do have anti-diabetes mellitus  
3 agents that are available. What are their  
4 limitations? Well, whether it be the sulfonylureas  
5 or the DPP-4 inhibitors or the metformin, over  
6 time -- over time -- the effectiveness of these  
7 agents tends to wane. And so you end up adding  
8 more and more agents, and eventually adding maybe  
9 injectables.

10 There is a failure to preserve beta cell  
11 function. You have the risk of hypoglycemia, which  
12 can be devastating to patients. And that  
13 particularly occurs with sulfonylureas or insulin  
14 therapy.

15 There's also the potential for weight gain.  
16 We again see that with sulfonylureas, the insulin,  
17 the thiazolidinediones. Gastrointestinal side  
18 effects with the GLP-1 receptor agonists, the  
19 metformin, other agents. And then you may get  
20 fluid retention, again with the sulfonylureas,  
21 insulin, and the thiazolidinediones.

22 So that's why there's been this focus of

1     saying, okay, we understand the pancreas. We  
2     understand the liver. We understand the muscle,  
3     and these types of things. But are there other  
4     organs that can help us and help us treat our  
5     patients?

6             What we've learned is the kidney -- the  
7     kidney -- may be an ally. And in fact, I believe  
8     this represents a paradigm shift. In the past, we  
9     always thought of the kidney as a victim, a victim  
10    of the diabetes mellitus, resulting in diabetes  
11    kidney disease. But in fact, I think the way we're  
12    viewing this now is that the kidney is potentially  
13    an ally in our treatment of diabetes mellitus and  
14    not just a victim of the consequences of diabetes  
15    mellitus.

16            So in conclusion, diabetes mellitus remains  
17    an epidemic with significant morbidity and  
18    mortality. Improvement in metabolic parameters are  
19    associated with improved outcomes. Numerous  
20    treatment options are available, but each have  
21    their limitations. And a need remains for new  
22    therapeutic options. Thank you.



**Sponsor Presentation - James List**

DR. LIST: Thank you, Dr. Bays.

Good morning. My name is Jim List. I lead the development program at Bristol-Myers Squibb. Dapa was designed to treat type 2 diabetes by targeting the kidney, taking advantage of the body's ability to excrete glucose in the urine. The kidney freely filters glucose from the bloodstream at the glomerulus, and that glucose is then brought back into the circulation by transporters in the proximal tubule. The majority of the glucose reabsorption is accomplished by sodium glucose co-transporter 2, or SGLT-2, and the remainder by SGLT-1.

The transport capacity of the system can be exceeded when the blood glucose level is high, such as in diabetes. When this happens, some of the excess glucose is excreted in the urine.

Dapa is a highly specific inhibitor of SGLT-2. It reduces the amount of glucose that is reabsorbed back into the body, and enhances the excretion of excess glucose into the urine.

1           This figure illustrates how the kidney  
2 handles glucose. The X axis represents the plasma  
3 glucose concentration, and the Y axis represents  
4 urinary glucose. As the plasma glucose rises, more  
5 and more glucose is filtered by the kidney.

6           At first, all of the filtered glucose is  
7 returned to the circulation. But when the plasma  
8 glucose rises beyond a threshold point of around  
9 180 milligrams per deciliter, excess glucose begins  
10 to appear in the urine.

11           In diabetes, this curve is shifted to the  
12 right, meaning that in patients whose blood sugar  
13 is already too high, the kidney paradoxically holds  
14 onto glucose more avidly. Dapa therapy shifts the  
15 curve to the left, causing more glucose to be  
16 excreted in the urine at any given plasma glucose  
17 concentration.

18           This directly lowers blood glucose  
19 independently of insulin. The excreted glucose  
20 brings with it calories, which leads to weight  
21 loss, an important treatment goal in type 2  
22 diabetes. And the diuretic effect of glucosuria,

1 combined with weight loss, leads to a lowering of  
2 blood pressure.

3 The pharmacokinetics and pharmacodynamics of  
4 dapa have been examined over a large range of  
5 doses, from 1 microgram, which has no effect, to  
6 500 milligrams, which is 50 times the proposed  
7 usual daily dose.

8 There is a clear and predictable  
9 relationship between dapa dose, shown here on the  
10 X axis, and 24-hour urinary glucose, shown on the  
11 Y axis. The blue curve represents healthy subjects  
12 and the red curve patients with type 2 diabetes.  
13 The diabetes curve lies higher than the healthy  
14 subject curve because patients with diabetes have  
15 higher blood sugars and therefore filter more  
16 glucose at the kidney.

17 The proposed usual daily dose of dapa is  
18 10 milligrams, which, as shown by the vertical  
19 dotted line, falls in the linear portion of the  
20 dose-response curve. As you will see, this dose  
21 provides meaningful efficacy with good safety and  
22 tolerability.

1           Dapa has well-characterized and predictable  
2       clinical pharmacology. This has been seen in  
3       studies of pharmacokinetics and pharmacodynamics,  
4       in 13 drug-drug interaction assessments, in  
5       specific patient populations, in exposure-response  
6       analyses, and in biopharmaceutical studies.

7           Together, this clinical pharmacology  
8       programs shows that dapa is well-tolerated at  
9       single doses up to 500 milligrams, and with daily  
10      dosing at up to 100 milligrams, with no effect on  
11      QT interval or heart rate.

12          Dapa is primarily metabolized through an  
13      inactive, stable, O-glucuronide. And dapa has  
14      characteristics that make it easy to use. Its  
15      pharmacokinetics and pharmacodynamics support  
16      once-daily dosing, with or without meals. There  
17      are no meaningful drug-drug interactions. And  
18      there's no need to adjust the dose in renal or  
19      hepatic impairment.

20          The clinical trials program looked at dapa  
21      across the diabetes spectrum. The studies included  
22      in the resubmission had more than 50 percent more

1 patient exposure than the original NDA filing, and  
2 more than 40 percent more than the 4-month safety  
3 update.

4 In this program, dapa was studied as  
5 monotherapy in drug-naive patients, as add-on  
6 therapy in patients failing other oral  
7 agents -- metformin, sulfonylurea, TZD, or DPP-4  
8 inhibitor -- and as add-on therapy in patients  
9 failing insulin-based regimens.

10 The program covered the continuum of  
11 diabetes progression and treatment intensification.  
12 Drug-naive patients in the monotherapy studies had  
13 a median duration of diabetes of less than 1 year,  
14 whereas at the other end of the spectrum, the  
15 patients on insulin-based regimens had a median  
16 duration of diabetes of more than 10 years.

17 In addition to these seven core placebo-  
18 controlled studies, dapa was also compared head-to-  
19 head against the sulfonylurea glipizide and against  
20 metformin in three active comparator trials; and  
21 it was studied in patients with relevant  
22 comorbidities -- overweight and obesity, moderate

1 renal impairment, cardiovascular disease, and  
2 poorly controlled hypertension.

3 There were also phase 2b exploratory studies  
4 and mechanism of action studies, and there were  
5 regional development programs in China and Japan.  
6 The resubmission included nine new studies along  
7 with additional long-term extension data from  
8 another four studies.

9 In the global clinical program, roughly a  
10 quarter of the patients came from the United  
11 States. These patients had demographics  
12 representative of the broader U.S. population. The  
13 mean age was in the mid-50s, with roughly 20  
14 percent of patients at or over age 65.

15 Gender, race, and ethnicity are shown. Of  
16 the U.S. patients, 12.4 percent were African  
17 American and 33.9 percent were Hispanic. Thus, the  
18 population studied represents the intended  
19 treatment population for dapa.

20 I would now like to invite Dr. Shamik Parikh  
21 to the podium to describe the efficacy of dapa, as  
22 demonstrated in the clinical trials program.

1 Dr. Parikh?

2 **Sponsor Presentation - Shamik Parikh**

3 DR. PARIKH: Thank you, Dr. List.

4 Good morning. My name is Shamik Parikh, and  
5 I lead the medical team for diabetes and metabolism  
6 at AstraZeneca.

7 In this overview of efficacy, I'll present  
8 efficacy data from two active-controlled studies,  
9 review data from placebo-controlled studies for  
10 glycemic efficacy, body weight, and blood pressure  
11 reduction, and present data supporting maintenance  
12 of efficacy of dapagliflozin in studies with long-  
13 term extensions.

14 We conducted two head-to-head trials with a  
15 10-milligram dose of dapagliflozin against two oral  
16 agents that are considered potent and are commonly  
17 prescribed in the United States, metformin and the  
18 sulfonylurea agent glipizide. Metformin, in  
19 particular, is used as the foundational initial  
20 therapy in most patients with type 2 diabetes.

21 The metformin combination and comparison  
22 study recruited drug-naive patients with poorly

1 controlled diabetes. The mean baseline A1c was  
2 9 percent.

3 Patients were randomized into one of three  
4 treatment groups -- the dapa 10-milligram  
5 monotherapy group, shown in orange; the met XR  
6 monotherapy group, shown in blue; or the  
7 combination group that received both dapa 10  
8 milligrams and met XR 2000 milligrams, shown in  
9 purple.

10 Treatment with dapa as initial combination  
11 therapy with metformin led to an absolute reduction  
12 in HbA1c of 2 percent units from baseline that was  
13 significantly better than A1c reduction with each  
14 individual monotherapy.

15 In the same trial, there was a prespecified  
16 test for noninferiority between the two monotherapy  
17 arms between dapa 10 milligrams and met XR  
18 2000 milligrams at week 24. Dapagliflozin met the  
19 prespecified noninferiority criteria, with a mean  
20 A1c reduction of 1.45 percent compared to 1.44  
21 percent reduction with metformin. This head-to-  
22 head comparison shows that dapagliflozin 10-



1 milligram results in HbA1c reductions similar to  
2 2000 milligrams of metformin XR.

3 Patients in this study were mostly  
4 overweight, with mean baseline body weight of  
5 88 kilograms. Change in body weight at week 24 was  
6 a secondary endpoint in the trial. Dapa was  
7 superior to metformin in reducing body weight.

8 By week 24, dapagliflozin treatment, shown  
9 in the orange bar on the left, reduced mean body  
10 weight by 2.7 kilograms, which was significantly  
11 greater than the weight reduction in the met XR  
12 group, shown in the middle. As shown on the right,  
13 the two treatments, given together, resulted in a  
14 weight loss of 3.3 kilograms from baseline, which  
15 was again significantly better than the weight loss  
16 achieved with metformin alone.

17 In addition to metformin, sulfonylureas are  
18 commonly prescribed and considered to be effective  
19 glucose-lowering agents. We compared dapagliflozin  
20 to glipizide, the most commonly-prescribed  
21 sulfonylurea agent in the United States, in a head-  
22 to-head study in patients with type 2 diabetes with

1 baseline A1c of 7.7 percent on a background of  
2 stable metformin therapy.

3 The primary objective was to compare changes  
4 in A1c between the two treatment groups at  
5 52 weeks. This study consisted of an initial 18-  
6 week titration period, during which the dose of  
7 dapagliflozin, shown in orange, was titrated up to  
8 10 milligrams and the dose of glipizide, shown in  
9 blue, was titrated to 20 milligrams, after which  
10 the doses were maintained.

11 During the titration period, glipizide had  
12 greater A1c reductions than dapagliflozin.  
13 However, there was waning of A1c reduction with  
14 glipizide after 18 weeks despite continued  
15 treatment. In contrast, dapagliflozin's reduction  
16 in A1c was maintained over 52 weeks. At the end of  
17 52 weeks, both treatments had identical A1c  
18 reduction of .52 percent that met the predefined  
19 noninferiority criteria.

20 Treatment with glipizide was associated with  
21 a more than tenfold increased risk of hypoglycemia  
22 compared to dapagliflozin. Over the 52-week

1 period, 41 percent of patients in the glipizide  
2 group had at least one episode of hypoglycemia,  
3 compared to 3.5 of patients in the dapa group.

4 Patients in this trial were mostly  
5 overweight and had a mean baseline body weight of  
6 88 kilograms. Dapagliflozin led to weight loss,  
7 whereas glipizide resulted in further weight gain.  
8 At the end of 52 weeks, there was a statistically  
9 significant difference of 4.6 kilograms, or  
10 10 pounds, between the two groups.

11 The proportion of patients with 5 percent or  
12 more weight loss from baseline was a predefined  
13 secondary endpoint in this study. At week 52, one-  
14 third of all dapa-treated patients had a weight  
15 loss of at least 5 percent from baseline compared  
16 to 2.5 percent of patients in the glipizide group.

17 The glycemic efficacy of dapagliflozin seen  
18 in active comparator trials was further supported  
19 from data from placebo-controlled studies of the  
20 relative changes in HbA1c, fasting plasma glucose,  
21 and postprandial glucose.

22 A1c reduction at week 24 versus placebo was

1 evaluated as a primary endpoint in seven placebo-  
2 controlled phase 3 studies conducted in the general  
3 type 2 diabetes population. Shown here are the  
4 changes in HbA1c in absolute percentage units from  
5 baseline.

6 On the left are two monotherapy studies in  
7 drug-naive patients with recent onset of type 2  
8 diabetes. In the middle are studies with dapag as  
9 add-on therapy to four different classes of oral  
10 antidiabetic agents. And towards the right is the  
11 study in patients with longer duration of diabetes  
12 being treated with insulin.

13 The predefined primary endpoint for HbA1c  
14 reduction was met in all of these trials. Both the  
15 doses tested, 5 and 10, were effective. The higher  
16 10-milligram dose, shown in orange, had a  
17 numerically better A1c reduction than 5-milligram  
18 dose in each of the five studies where the two  
19 doses were tested side by side.

20 Due to the mechanism of action of  
21 dapagliflozin, it was expected that renal  
22 impairment or decreased renal function that leads

1 to reduced glucose filtration would lead to  
2 decreased efficacy with dapagliflozin.

3 We tested dapa as add-on treatment in  
4 patients with type 2 diabetes and moderate renal  
5 impairment. All patients in this study had an eGFR  
6 or between 30 and 60 mL per minute per 1.73 meters  
7 squared. The primary endpoint was HbA1c reduction  
8 at week 24.

9 A1c reductions from baseline of .41 and  
10 .44 percent were observed with 5- and 10-milligram  
11 treatment groups, respectively. The placebo group  
12 also had a reduction of .32 percent, leading to a  
13 nonsignificant placebo-corrected reduction in the  
14 dapa treatment groups.

15 This study in patients with moderate renal  
16 impairment therefore did not meet its primary  
17 endpoint. Based on this data and the association  
18 between renal function and the mechanism of action,  
19 we have proposed not initiating dapagliflozin in  
20 patients with eGFR below 60.

21 Besides HbA1c, fasting plasma glucose, or  
22 FPG, is a commonly monitored parameter by

1 healthcare providers in clinical practice.

2 Displayed here are the FPG reductions in the seven  
3 placebo-controlled phase 3 studies previously shown  
4 for Alc.

5 A statistically significant and clinically  
6 relevant placebo-corrected decrease of between 20  
7 and 30 milligrams per deciliter in FPG was observed  
8 in dapagliflozin treatment across all studies. FPG  
9 reductions were numerically better with the  
10 10-milligram versus the 5-milligram dose in each of  
11 the five trials where both the doses were tested.

12 Treatment with dapa was also associated with  
13 reductions in postprandial glucose. Four phase 3  
14 studies evaluated postprandial glucose, or PPG,  
15 lowering. There were significantly greater  
16 reductions in two-hour PPG values from baseline  
17 versus placebo at week 24 in each of these four  
18 studies.

19 Over 90 percent of the study subjects in our  
20 phase 3 studies were overweight at baseline, with a  
21 mean baseline body weight ranging from 85 to  
22 95 kilograms. Shown here is the predefined

1 secondary endpoint of body weight change at week 24  
2 in the seven placebo-controlled studies. A  
3 reduction in body weight at week 24 was observed  
4 with dapa treatment across the studies.

5 In the add-on to TZD trial, which is the  
6 second trial from the right, dapagliflozin  
7 mitigated the weight gain from ongoing pioglitazone  
8 therapy. In order to better characterize this  
9 weight loss effect, particularly the relative  
10 contribution of fluid loss versus fat loss, we  
11 conducted the dual X-ray absorptiometry, or DEXA,  
12 study to specifically evaluate changes in body  
13 composition along with changes in body weight.

14 The primary endpoint was change in body  
15 weight at week 24 between dapa 10 milligrams and  
16 placebo on background of stable metformin therapy.  
17 As shown here, dapa 10 milligrams per day led to a  
18 gradual reduction in body weight of 3 kilograms  
19 from baseline that had not plateaued by week 24.  
20 The difference of 2.1 kilograms between dapa and  
21 placebo groups was statistically significant.  
22 Changes in body composition were assessed with

1 whole-body DEXA scans done at baseline and at  
2 week 24.

3 Shown here are the relative changes for fat  
4 mass and lean mass between dapa and placebo  
5 treatment groups. There was a statistically  
6 significant and clinically relevant decrease in fat  
7 mass of 2.2 kilograms in the dapa group, as shown  
8 in the first bar, compared to .7 kilograms of fat  
9 loss in the placebo group, shown in the second bar.

10 Two-thirds of the weight loss in the dapa  
11 group was due to fat loss. The remaining one-third  
12 was accounted by change in lean mass that included  
13 changes in the fluid compartment. This study  
14 showed that weight loss with dapagliflozin is  
15 primarily attributable to a reduction in body fat  
16 mass.

17 Along with caloric loss resulting from  
18 glucosuria, dapagliflozin also leads to mild  
19 osmotic diuresis. Modest reductions in systolic  
20 blood pressure were observed with dapagliflozin  
21 across our phase 3 studies, particularly in those  
22 patients who were hypertensive at baseline.



1           To further elucidate the effect on blood  
2     pressure, we have recently completed two 12-week-  
3     duration studies in hypertensive patients with  
4     type 2 diabetes. All patients in these two studies  
5     were treated with standard of care antihypertensive  
6     background therapy such as ACE inhibitors or  
7     angiotensin receptor blockers.

8           The study on right also required patients to  
9     be on additional antihypertensive therapy at  
10    baseline besides ACE inhibitors or ARPs. The mean  
11    baseline systolic blood pressure was approximately  
12    150 millimeters of mercury across these two  
13    studies.

14          As shown here, the absolute reduction in  
15    seated systolic blood pressure ranged from between  
16    10 to 12 millimeters of mercury for the  
17    dapagliflozin treatment arms, with a statistically  
18    significant placebo-subtracted difference of 3 to  
19    4 millimeters of mercury across both studies.

20          The data from these trials indicate that  
21    dapagliflozin, in addition to glycemic and weight  
22    benefit, leads to modest reductions in systolic

1 blood pressure, particularly in hypertensive  
2 patients.

3 For a drug being evaluated for management of  
4 a chronic, progressive disease such as type 2  
5 diabetes, it is important to a certain maintenance  
6 of pharmacodynamic effect over longer durations.  
7 Shown here is the change in urine glucose excretion  
8 from baseline expressed as gram-per-gram of  
9 glucose-to-creatinine ratio over the 2-year  
10 duration of the head-to-head study versus  
11 glipizide. Dapagliflozin induced an increase in  
12 mean urine glucose excretion from baseline that was  
13 maintained for the duration of the trial.

14 In the same study, the decrease in HbA1c  
15 with dapagliflozin seen at 52 weeks was sustained  
16 long-term with arguably a small attenuation of  
17 effect at the later visits. On the other hand, in  
18 the glipizide treatment group, the waning of effect  
19 seen following 18 weeks of treatment continued with  
20 little or no clinically meaningful effect seen at  
21 week 104. At week 104, the difference between the  
22 two treatment arms was .18 percent in favor of

1       dapagliflozin.

2               Another parameter for assessing long-term  
3       glycemic control is to compare the proportion of  
4       patients who had to be discontinued due to poor  
5       glycemic control based on prespecified glycemic  
6       criteria.

7               As shown here, fewer patients had to be  
8       discontinued due to inadequate glycemic control  
9       with dapagliflozin treatment compared to glipizide  
10      in both the first and second years of the study,  
11      indicating better glycemic control with  
12      dapagliflozin over the 2-year period.

13              In addition to glycemic control, the  
14      reduction in body weight with dapa at 52 weeks was  
15      persistent through week 104. Patients in the  
16      glipizide group, on the other hand, retained their  
17      weight gain over the 2-year period. At the end of  
18      2 years, dapagliflozin-treated patients, on  
19      average, weighed 5 kilograms less than the  
20      glipizide-treated patients.

21              Because of the progressive nature of type 2  
22      diabetes and the potential for dapagliflozin to be

1       used in patients already treated with insulin, we  
2       evaluated change in insulin requirements in the  
3       long-term extension of the add-on to insulin trial.

4               Illustrated here are the changes to mean  
5       daily insulin doses over 2 years in the placebo and  
6       dapa treatment groups. The mean baseline insulin  
7       use was 77 units per day in both groups. Increase  
8       in insulin doses during the study was only allowed  
9       as a rescue treatment based on predefined glycemic  
10      criteria.

11             The mean daily insulin requirement in the  
12      placebo group, shown in grey line, increased by  
13      approximately 5 units at 6 months, 10 units at  
14      1 year, and 19 units by week 104. In contrast, no  
15      change in mean daily insulin use was observed in  
16      the dapagliflozin treatment group over the 2-year  
17      period.

18             In conclusion, treatment with dapagliflozin  
19      10 milligrams led to HbA1c reductions equivalent to  
20      oral antidiabetic agents such as metformin and  
21      sulfonylureas while displaying a low intrinsic risk  
22      of hypoglycemia, with the additional benefit of

1 weight loss.

2 Dapagliflozin was effective in lowering  
3 HbA1c in a broad range of patients with type 2  
4 diabetes, regardless of disease duration and  
5 background antidiabetic therapy.

6 Consistent with its mechanism of action, the  
7 glycemic efficacy of dapagliflozin is dependent on  
8 baseline renal function and is attenuated in  
9 patients with reduced renal function.

10 Exploratory long-term analysis supported  
11 maintenance of glycemic efficacy over 2 years in  
12 both active comparator and placebo-controlled  
13 studies. Dapagliflozin treatment led to sustained  
14 reduction in body weight, mainly due to a reduction  
15 in body fat mass. Treatment with dapa was also  
16 associated with meaningful reductions in systolic  
17 blood pressure in hypertensive patients.

18 In patients with type 2 diabetes on  
19 relatively high doses of insulin where often the  
20 last resort for healthcare providers for achieving  
21 or maintaining glycemic control is to further  
22 increase the insulin doses, dapagliflozin mitigated

1 the need for increasing insulin dose over a 2-year  
2 period. Thank you.

3 I now invite Dr. Jim List to take you  
4 through the safety profile for dapagliflozin.

5 **Sponsor Presentation - James List**

6 DR. LIST: Thank you, Dr. Parikh.

7 For the safety topics, first we will  
8 describe the pooling of data from the clinical  
9 studies for the safety analyses. Next we will  
10 present general safety and some key effects of the  
11 SGLT-2 inhibitor class.

12 We will then spend the bulk of the safety  
13 presentation on three topics of special interest:  
14 hepatic safety, malignancy assessment, and  
15 cardiovascular safety.

16 The clinical safety profile of dapa was  
17 characterized by pooling data across studies. At  
18 the top is the all phase 2b and 3 pool. This is  
19 the largest pool, comprising data from 21 studies  
20 with durations ranging from 12 to 208 weeks. This  
21 pool was used to characterize rare events such as  
22 deaths, malignancies, and cardiovascular events.

1           The only fully submitted studies that were  
2 not included in this pool are a Japanese open-label  
3 study, excluded because it lacked a control arm,  
4 and two blood pressure studies that were completed  
5 after the database cutoff for the safety pools.

6           In the middle is a subset of the all  
7 phase 2b and 3 pool, comprising 13 placebo-  
8 controlled studies. Data from these 13 studies, up  
9 to the primary endpoint of each study at 12 or  
10 24 weeks, were the basis of the placebo-controlled  
11 short-term pool analyses.

12           This placebo-controlled short-term pool is  
13 our best controlled safety data set. It excludes  
14 data from extensions after the primary endpoint to  
15 avoid confounding by dropouts and rescue  
16 medications. It excludes active comparator studies  
17 to allow for a clean placebo comparison. And it  
18 excludes studies not clearly generalizable to the  
19 intended U.S. treatment population, such as Chinese  
20 and Japanese phase 3 studies, studies of special  
21 patient populations, and studies that don't include  
22 the proposed usual 10-milligram dose.

1           At the bottom of the figure, of the  
2       13 studies in the placebo-controlled short-term  
3       pool is the nested subset of nine studies that had  
4       long-term extensions beyond the primary endpoint.  
5       The long-term data from these nine studies, which  
6       we call the placebo-controlled short-term plus  
7       long-term pool, were assessed and compared to the  
8       placebo-controlled short-term pool to confirm the  
9       safety profile of dapa with longer exposures up to  
10      104 weeks.

11           Turning to general safety, the percentage of  
12      patients having at least one adverse event was  
13      60 percent for dapa 10 milligrams and 55.7 percent  
14      for placebo. Serious adverse events, adverse  
15      events leading to discontinuation, and, at the  
16      bottom, deaths, were balanced with control.

17           Shown here are the 12 most common adverse  
18      events in the clinical program, seen in at least  
19      2 percent of patients in either treatment group,  
20      dapa 10 milligrams or placebo. Five of these were  
21      more common on dapa than placebo. Three of these  
22      5 may plausibly be related to glucosuria, urinary



1 tract infection, dizziness, and pollakiuria, which  
2 means frequent urination.

3 Hypoglycemia was similar in frequency to  
4 placebo in monotherapy or in combination therapy,  
5 except when dapa was added to sulfonylurea or to  
6 insulin, where the frequency was higher on dapa.  
7 Thus, while dapa appears to have a low intrinsic  
8 risk of hypoglycemia, it can enhance the  
9 hypoglycemic tendencies of insulin or insulin  
10 secretagogues.

11 An increase in urogenital infections as a  
12 result of glucosuria is a class effect of SGLT-2  
13 inhibitors. In patients treated with dapa compared  
14 to placebo, urinary tract infections were slightly  
15 more common at 4.7 percent versus 3.5 percent, and  
16 genital infections were clearly more common at  
17 5.5 percent versus 0.6 percent. These infections  
18 were generally graded as mild to moderate, and  
19 responded to an initial course of therapy without  
20 interrupting dapa treatment.

21 At the bottom, there was no increase in the  
22 more serious infections. Pyelonephritis, serious

1 adverse events of urinary tract infection, and  
2 serious adverse events of genital infection were  
3 all rare and balanced with control.

4         Glucosuria causes osmotic diuresis. With  
5 SGLT-2 inhibitors, as with other diuretic classes,  
6 volume depletion can occur. With dapa, adverse  
7 events of volume depletion were uncommon. These  
8 events were seen in 1.1 percent of patients on dapa  
9 10 milligrams versus 0.7 percent on placebo. These  
10 events were more common in older patients, patients  
11 with moderate renal impairment, and patients on  
12 loop diuretics.

13         The volume depletion events generally did  
14 not have serious sequelae. At the bottom, the  
15 events that matter most clinically, those  
16 categorized as serious adverse events, were  
17 balanced with control.

18         Renal function was stable with dapa therapy.  
19 Here dapa is shown in orange out to 102 weeks of  
20 follow-up. After an initial clinically  
21 insignificant downward adjustment in the eGFR,  
22 there was a return to baseline and stability over

1 time.

2 The diuretic effect of SGLT-2 inhibitors and  
3 the associated fluid shifts can cause transient  
4 increases in serum creatinine. Adverse events  
5 related to renal function occurred in 3.2 percent  
6 of patients on dapa 10 milligrams and 1.8 percent  
7 of patients on placebo. These events largely  
8 consisted of relatively small increases in serum  
9 creatinine and they were reversible, with most  
10 patients returning to baseline.

11 They were more common in older patients, and  
12 especially in patients with moderate renal  
13 impairment. There were no events of acute tubular  
14 necrosis or acute nephritis, and no increase in  
15 proteinuria with dapa therapy. At the bottom,  
16 serious adverse events related to renal function  
17 were few and balanced between dapa and control.

18 The risk for fractures with long-term use is  
19 a safety consideration that was raised for the  
20 approved SGLT-2 inhibitor canagliflozin. In the  
21 dapa program, there was no overall increase in  
22 fractures in the short-term or long-term

1       experience, and there was no effect of dapa  
2       treatment on bone density.

3               With dapa therapy, there were no clinically  
4       meaningful mean changes in the concentrations of  
5       the major serum electrolytes or of calcium,  
6       magnesium, phosphorus, or parathyroid hormone.

7       Hyperkalemia was similar in dapa to placebo.

8       Unlike the approved SGLT-2 inhibitor canagliflozin,  
9       increases in hyperkalemia were not seen in patients  
10      with renal impairment or in patients on ACE  
11      inhibitors or potassium-sparing diuretics.

12             As with other members of the class, dapa was  
13      associated with a decrease in serum uric acid and a  
14      small increase in hematocrit.

15             Increases in LDL cholesterol and non-HDL  
16      cholesterol have been reported with canagliflozin  
17      and appear to be a class effect, at least  
18      directionally. With dapa, these changes were  
19      small.

20             There was a 2.5 percent increase from  
21      baseline in mean total cholesterol, a 2.9 percent  
22      increase in LDL cholesterol, and a 1.3 percent

1 increase from baseline in non-HDL cholesterol.

2 There was also an increase in HDL cholesterol and a  
3 decrease in triglycerides.

4 Moving to hepatic safety, when presenting  
5 data to this committee in 2011, the FDA noted a  
6 single clinical case of potential drug-induced  
7 liver injury. There were no preclinical liver  
8 safety signals and no other clinical liver safety  
9 signals.

10 Liver test abnormalities with dapa have been  
11 balanced with control. Shown here are the  
12 proportions of patients experiencing liver test  
13 elevations of aminotransferase, bilirubin, combined  
14 aminotransferase and bilirubin, or of alkaline  
15 phosphatase. For each of these parameters, there  
16 was no meaningful difference between dapa and  
17 control.

18 Combined elevations of both aminotransferase  
19 greater than three times the upper limit of normal  
20 and bilirubin greater than two times the upper  
21 limit of normal are of particular importance in  
22 evaluating liver safety.

1           In the dapa program, these cases were  
2       balanced with control at 7 cases, or 0.1 percent,  
3       for dapa and 4 cases, also 0.1 percent, for  
4       control. None of these cases of combined  
5       elevations was adjudicated as probably related to  
6       study drug, and each of the cases had a more likely  
7       alternative diagnosis.

8           The alternative diagnoses for the cases of  
9       combined elevations, shown here, were autoimmune  
10      hepatitis, gallstone disease, pancreatic cancer,  
11      septic shock, and viral syndrome. The case with  
12      the alternative diagnosis of autoimmune hepatitis  
13      was a case highlighted as a particular concern by  
14      the FDA. New data mitigates the concern around  
15      this case.

16           Here's what we knew about the case at the  
17      time of the 2011 advisory committee meeting. The  
18      patient, a 78-year-old male, was receiving  
19      metformin and dapagliflozin 2.5 milligrams,  
20      titrated to 5 milligrams daily. At baseline, the  
21      patient had a slightly elevated ALT. On day 127,  
22      his ALT began rising, peaking along with bilirubin

1 at day 200. On day 192, dapa was discontinued.  
2 After discontinuation of dapa, his ALT dropped and  
3 stabilized between 10 and 15 times the upper limit  
4 of normal.

5 A liver biopsy was performed, and read as  
6 compatible with the differential diagnosis of viral  
7 agents, drugs, and autoimmune hepatitis, and the  
8 biopsy report noted that a number of histological  
9 features favored the diagnosis of autoimmune  
10 hepatitis. Autoimmune serologies were negative,  
11 but immunoglobulins were elevated.

12 On day 349, immunosuppressive therapy with  
13 prednisolone was initiated to treat presumptive  
14 autoimmune hepatitis. This was followed by marked  
15 improvements in the patient's liver tests. The  
16 immunosuppressive regimen was then switched to  
17 azathioprine, with liver tests returning to  
18 baseline.

19 That's what we knew about this case at the  
20 time of the last advisory committee meeting. Three  
21 expert hepatologists adjudicating the case in a  
22 blinded manner offered three different opinions,

1 one adjudicating the case as probably related, one  
2 as possibly related, and one as unlikely related to  
3 study drug. Their consensus adjudication at that  
4 time was possibly related.

5 Since that time, over a total of 3 and a  
6 half years of follow-up, the patient was found to  
7 continue to have active liver disease. He had two  
8 further flares in liver tests, peaking at days 714  
9 and 1132. At the last data point, the patient  
10 continued to receive immunosuppressive therapy and  
11 carried a clinical diagnosis of autoimmune  
12 hepatitis.

13 Autoimmune hepatitis can be idiopathic or it  
14 can be triggered by drugs. Atorvastatin, for  
15 example, on very rare occasion can do this, and  
16 notably, the patient was taking atorvastatin.

17 It's difficult to differentiate idiopathic  
18 from drug-induced autoimmune hepatitis. One  
19 notable point of differentiation is that drug-  
20 induced autoimmune hepatitis tends not to relapse  
21 after the offending agent is discontinued, which  
22 does not fit this patient's clinical picture.



1           Given the chronic relapsing nature of the  
2     patient's disease after discontinuation of dapa, a  
3     role for dapa triggering the autoimmunity is  
4     unlikely. The probable diagnosis in this case is  
5     idiopathic autoimmune hepatitis.

6           In summary, with dapa, there has been no  
7     preclinical liver significant, no increases in  
8     liver test abnormalities. In all cases, combined  
9     elevations of aminotransferase and bilirubin have  
10    probable alternative diagnoses. Taken together,  
11    the data do not show a signal for risk of drug-  
12    induced liver injury.

13          Turning now to malignancy assessment, in the  
14    dapa clinical program there was no overall  
15    imbalance in malignancies. The Kaplan-Meier plots  
16    of time to malignancy show matched curves for dapa  
17    and control. With increasing time of exposure,  
18    there's no upward inflection in the dapa curve, as  
19    might be seen with a cancer-causing agent.

20          Shown here are the incidence rate ratio and  
21    95 percent confidence intervals for malignancies by  
22    tumor type. At the top are overall malignancies,

1 with an incidence rate ratio of 1.03. When we  
2 break this down by tumor type, we see, as expected,  
3 variability across equilibrium. Some tumor types  
4 were more frequent on dapa than control -- those  
5 are the ones with point estimates to the right of  
6 the vertical line -- and some tumor types were more  
7 frequent on control than dapa. Those are the ones  
8 with point estimates to the left of the vertical  
9 line. No individual tumor type was in perfect  
10 balance between dapa and control, and none of the  
11 imbalances was statistically significant.

12 The distribution appears to be random,  
13 without a unifying anatomic or functional  
14 explanation. For example, bladder cancer, near the  
15 top of the figure, had a point estimate to the  
16 right of the vertical line, favoring control. On  
17 the other hand, renal tract cancer, near the bottom  
18 of the figure, had a point estimate to the left of  
19 the vertical line, favoring dapa.

20 Similarly, breast cancer, near the top of  
21 the figure, had a point estimate to the right of  
22 the vertical line, while female reproductive

1 cancer, near the middle of the figure, had a point  
2 estimate to the left of the vertical line.

3 Of note, in our NDA resubmission, since the  
4 2011 advisory committee meeting, there were 5 new  
5 breast cancer cases, which led to a fall in the CDC  
6 rate ratio for breast cancer from 4.4 to 2.5. This  
7 illustrates the instability of incidence rate  
8 ratios when dealing with small numbers of cases.

9 For bladder cancer, there were no new cases  
10 in the submitted database. The only new bladder  
11 cancer case occurred in an ongoing trial, which was  
12 not part of the refiling and which is noted in the  
13 footnote to the figure.

14 Taking this new case into account, that  
15 leaves us with 10 bladder cancer cases on dapa and  
16 one on control. With nearly twice as many patients  
17 randomized to dapa as control, this gives us an  
18 incidence rate ratio of bladder cancer of  
19 roughly 6.

20 Looking at the epidemiology, bladder cancer  
21 is more common in older patients, in males, and in  
22 patients with diabetes. We calculated the expected

1 incidence rate, adjusting for these three factors.  
2 With these adjustments, the expected number of  
3 bladder cancer cases on dapa is 4, and on control  
4 is nearly 3. Thus, while the imbalance in bladder  
5 cancer cases clearly reflects having more cases  
6 than expected on data, it's further inflated by  
7 having less cases than expected on control.

8 Dr. Dean Bajorin, professor of medicine at  
9 Cornell Medical College and practicing oncologist  
10 at Memorial Sloan-Kettering Cancer Center, will now  
11 provide his clinical assessment of the individual  
12 cases of bladder cancer in the dapa program and how  
13 they relate to what is known about bladder cancer  
14 biology.

15 Dr. Bajorin?

16 **Sponsor Presentation - Dean Bajorin**

17 DR. BAJORIN: I'm Dean Bajorin. I'm a  
18 medical oncologist at Memorial Sloan-Kettering  
19 Cancer Center. I oversee the bladder cancer  
20 program for patients with advanced disease. I am a  
21 paid consultant by the sponsor, and my institution  
22 received research funding from the sponsor. But I

1 have no financial interest in your deliberations.

2           So to understand the bladder cancer cases,  
3 I'd like to first really give you a little bit of  
4 understanding of bladder cancer itself. This is a  
5 schematic of the bladder cancer wall. At the top  
6 is the interior of the bladder. At the bottom is  
7 the outside of the bladder. And the wall is made  
8 up of several components, the mucosa, where all  
9 cancers start; the lamina propria, the first level  
10 of invasion; and then the muscularis propria, which  
11 is the muscle that controls urination.

12           We break these tumors down into two major  
13 categories, what we call the superficial or non-  
14 muscle-invasive disease; they occur in the  
15 superficial aspects. You'll see on the left it's  
16 the Ta tumors. The middle one is Tis for in situ  
17 disease, and T1 is just breaking into the lamina  
18 propria.

19           The second major category of these tumors is  
20 muscle-invasive tumors, from T2 through T4, and  
21 it's in the bladder or beyond the bladder. It's  
22 really important to note that every single one of

1       these tumors starts in the mucosa and then, in the  
2       case of Tis and T1, progress into further stages  
3       down into the muscle. From a clinical point of  
4       view, the time to development from the in situ to  
5       the T1 disease, for example, the median time is  
6       about a year in modern studies.

7               The Ta tumors are the most curable of  
8       tumors. They actually grow into the lumina, the  
9       bladder, and not deeply into the muscle of the  
10      bladder. And so they have a survival rate of  
11      around 98 to 99 percent. They're low-grade  
12      lesions, for the most part. On the opposite end of  
13      the spectrum are the muscle-invasive tumors. Their  
14      survival is 40 to 60 percent. They can invade into  
15      the local structures.

16             But common to all the tumors is that they  
17      are on the surface of the mucosa, they are exposed  
18      to the urine, and they are vascular tumors, and  
19      they bleed and they bleed intermittently. And so  
20      blood in the urine, or hematuria, is a common way  
21      of detecting this disease.

22             So there are studies looking at hematuria as

1 a screening tool, and the best studies are from Ed  
2 Messing and colleagues. And I'll draw your  
3 attention to the bottom line, where men over 50  
4 were given urine tests daily for 5 days and then  
5 weekly for a year, and any positive urine, trace or  
6 higher, was considered an indication for working up  
7 for bladder cancer because that is the standard of  
8 care. In this case, 1575 men were screened, 258  
9 had hematuria, and 8 percent had bladder cancer.

10 What it demonstrates is it's a sensitive  
11 marker for detecting the disease, but it's not  
12 specific because there are other causes of  
13 bleeding, including infection and renal stones.  
14 But it's important when we examine these cases.

15 These are all the cases that  
16 developed -- or, excuse me, that were detected  
17 while on dapagliflozin. In the red diamond is the  
18 first evidence of hematuria, and in the blue circle  
19 is the diagnosis of bladder cancer.

20 So you see in these timelines that 7 out of  
21 the 10 patients had hematuria before ever receiving  
22 the study drug, and 2 additional patients had

1       hematuria in the first 6 months, making a  
2       compelling case that these may be preexisting  
3       tumors.

4               But let's take a look at them as a  
5       composite. The first observation with regard to  
6       these 10 patients is the following, is that they  
7       are predominately male over 50. Eight of the  
8       10 patients had significant tobacco exposure. So  
9       let's put that into perspective. Each pack-year is  
10      7,000 cigarettes, so someone with 100 pack-years  
11      has had 700,000-cigarette exposure prior to going  
12      on the study drug.

13              We know that bladder cancer predominates in  
14      males, and that bladder cancer increases with  
15      increasing number of smoking years and the daily  
16      number of cigarettes. This is not to say that the  
17      arms are in balance with regard to smoking, but it  
18      is to say that these patients have predisposing  
19      risk factors with regard to this disease.

20              The next observation is the time at which  
21      the diagnosis was made, and you see the diagnosis  
22      month. And it's quite brief, actually, on study.



1 Five of the 10 cases occurred within 6 months of  
2 the study drug, and another 5 cases between 12 and  
3 24 months.

4 That's an important observation because if  
5 we look at a known carcinogen that causes cancers  
6 in the clinic, which is cyclophosphamide, we have  
7 data from a long-term study of Wegener's  
8 granulomatosis, and cyclophosphamide had a 31-fold  
9 increase in bladder cancer compared with SEER data.  
10 And the median duration of cyclophosphamide  
11 treatment was 2.7 years, and the median time to the  
12 development of tumors was in the 8- to 10-year  
13 range. That's very different for the study drug.

14 The next observation is the T stages of the  
15 tumors. You'll see in the first bracket, the top  
16 bracket, that the majority of these patients had Ta  
17 or T1 disease, called superficial tumors. If we  
18 look at the demographics of the 60,000 people who  
19 develop bladder cancer in the United States per  
20 year, three-quarters, 75 percent, have superficial  
21 disease, and in this instance, 8 of 10 on dapa had  
22 superficial disease.

1           The second bracket is the T2 patient, and if  
2       we look at muscle-invasive disease in the United  
3       States, about 20 percent of tumors each year  
4       develop muscle-invasive disease, 1 in 10 for dapa.  
5       Then the third bracket is the patient with  
6       metastatic disease, and it's about 5 percent of all  
7       comers in the United States. And so if we look at  
8       these numbers, the distribution of these different  
9       bladder cancers is similar to the patient  
10      population at large.

11           So let's take a look, an in-depth look, at  
12      each one of the patients. The first set of  
13      patients are the stage 0a patients. These are the  
14      patients with papillary tumors that grow into the  
15      lumina of the bladder. Shown in yellow are 2  
16      patients, and I will walk you through the patients  
17      and focus on the reason for the workup in the  
18      additional clinical information.

19           So the 48-year-old male from the U.S., this  
20      tumor was discovered on an incidental CT scan in a  
21      workup for coronary artery disease. And in fact,  
22      this patient also had hematuria before starting on

1 the study drug.

2 The 60-year-old from Canada, it also was an  
3 incidental finding during a cystoscopy when being  
4 evaluated for bladder -- excuse me, for renal  
5 stones. This patient also had preexisting  
6 hematuria.

7 The next patient is a 53-year-old from  
8 Slovakia. She had a urinary tract infection and  
9 hematuria at the same time, sponsoring the workup.

10 These three patients had hematuria. The  
11 first one had microscopic hematuria, but we see in  
12 the chart that this patient had hematuria from day  
13 minus 165. And the two other patients, the 66-  
14 year-old from the U.S., had gross painless  
15 hematuria, but this patient had recurrent hematuria  
16 on days 56, 84, 118, and 377. And the 67-year-old  
17 from Hungary also had gross hematuria, but this  
18 patient also had multiple episodes of hematuria,  
19 including day 1, week 1, and 7 of the 9 urines were  
20 positive in the first 12 months.

21 Let's examine the stage 1 patients. The 55-  
22 year-old from Taiwan, diagnosed at 6 months,

1 presented to the urologist's office with hematuria  
2 intermittently for 3 months and persistent  
3 hemospermia. This patient had trace blood on day  
4 minus 36, day 1, and trace blood in 5 of the  
5 8 tests while on study.

6 The 76-year-old from Germany presented with  
7 gross hematuria at 24 months, but there were no  
8 preexisting or on-study blood urines. And so this  
9 is a de novo case for which we have no preexisting  
10 indications.

11 The next case is a 67-year-old from  
12 Argentina, discovered at 5 months with gross  
13 hematuria. However, this patient had trace blood  
14 in the urine on day 1, 2-plus on week 2, multiple  
15 positive urines, a urinary tract infection on  
16 day 84, gross hematuria on day 130, urinary urgency  
17 and frequency, and then came to diagnosis on  
18 day 144 with an 80 by 60 millimeter mass, which is  
19 far too large to have occurred during this time  
20 period.

21 Last is the 75-year-old from Japan,  
22 diagnosed actually at 1.5 months because of a

1 positive occult urine on day 36. But this patient  
2 had positive urines dating back to day minus 215,  
3 and had hematuria in 6 determinations done in the  
4 first 1 and a half months, and had symptoms of  
5 anorexia and weight loss at day 30 on the study  
6 drug and metastasis at diagnosis when first  
7 discovered.

8           So in my opinion, it's clinically impossible  
9 that dapagliflozin caused all these cancers, for  
10 the following reasons. The tumors observed are the  
11 same as those seen in the general population.  
12 Hematuria was present either before or very shortly  
13 after starting dapa, suggesting preexisting  
14 lesions, and multiple episodes of hematuria after  
15 that reinforced that concept.

16           Drug exposure and the time to cancer  
17 detection were shorter than expected with known  
18 carcinogens, which are generally in years in what  
19 we see in the clinic. And then both tumor  
20 initiation and the time to progression of the  
21 disease are inconsistent with the clinical behavior  
22 of bladder cancer.

1           Lastly, the clinical data do not support the  
2 rapid growth of preexisting lesions. If we  
3 hypothesize that these lesions were evident at the  
4 time of the study, did dapa cause an increase in  
5 growth to come to detection?

6           So we go back to the clinical data again.  
7 And as you recall, several of these cases were  
8 incidental. There were several cases also that had  
9 gross hematuria. And you could hypothesize, well,  
10 perhaps the tumor grew rapidly and caused the gross  
11 hematuria. But if you examine the charts, several  
12 of these patients are actually on aspirin,  
13 increasing the likelihood of bleeding.

14           Then lastly is that what you see sprinkled  
15 through many of these cases is actually a failure  
16 to detect bladder cancer and not realize the  
17 symptoms may represent cancer.

18           The other issue is the following, and that  
19 is the actual biology of the tumor related to the  
20 disease. We talked earlier about Ta tumors and how  
21 they're slow-growing, they grow into the lumen, and  
22 they have a high likelihood of cure. At the other

1 end of the spectrum on the bottom right are those  
2 patients who have aggressive tumors. These tend to  
3 invade, and actually have a high likelihood of  
4 incurability.

5 But we know that these tumors are not just  
6 different in how they are staged and how they  
7 behave; biologically, they're very different. And  
8 you'll see here what is considered a divergent  
9 pathway, from the normal urothelium into cancer.

10 The top pathway are these tumors that grow  
11 into low-grade papillary tumors. They go through a  
12 phase of hyperplasia and then into a low-grade  
13 tumors. And they have mutations that are  
14 associated with them, such as HRAS and FGFR3  
15 mutations.

16 But the bottom pathway are the ones that go  
17 through the carcinoma in situ, the more high-grade  
18 lesions, and then into invasive tumors. These tend  
19 to have a very high degree of mutations of p53 and  
20 RB, and do not frequently have the FGFR3 mutations.

21 Now, this is a gross oversimplification of  
22 what we know about the biology of this disease

1       because there are many mutations and alterations  
2       that we see in these family of diseases. But the  
3       point I want to make is that there's no one  
4       unifying growth factor for each one of these  
5       cancers. And the second thing in studies that we  
6       have to date, up to and including whole genome  
7       sequencing, is that we have not seen the SGLT-2  
8       gene implicated in the biology of these diseases.

9               Back to you, Jim.

10               **Sponsor Presentation - James List**

11               DR. LIST: Thank you, Dr. Bajorin.

12               In considering cancer risk, we look at the  
13       possibility of off-target effects. Dapa is highly  
14       selective for SGLT-2, which is not expressed in the  
15       bladder, and dapa has no meaningful pharmacologic  
16       activity at more than 300 targets assessed.

17               We further assessed cancer risk through our  
18       comprehensive preclinical program, which included  
19       studies that addressed both carcinogenicity and  
20       tumor promotion. Of note, all agents known to  
21       cause bladder cancer in humans elicit signals in  
22       these models.



1           The core studies in this preclinical program  
2       are shown here. Going left to right, there are  
3       studies of genetic toxicity, subchronic and chronic  
4       toxicology, carcinogenicity, reproductive  
5       toxicology, special investigations of tumor  
6       promotion, and finally, at the far right, studies  
7       developing the methodology needed to carry out  
8       further tumor promotion studies of the type  
9       highlighted by the FDA in their formal dispute  
10      resolution response letter as being reasonable to  
11      conduct in the postmarketing period.

12           These studies looked at the effects of dapa  
13      and its metabolites. They looked at the effects of  
14      changes in urine composition. And they looked at  
15      the effect of the combination of dapa with changes  
16      in urine composition.

17           We concur with the FDA's assessment that  
18      dapa is not a carcinogen. The genetic toxicology  
19      and carcinogenicity studies show that dapa is not  
20      genotoxic or carcinogenic even at high exposure  
21      multiples. This agrees with the clinical data,  
22      which as Dr. Bajorin outlined, indicate that the

1 bladder cancer cases in the dapa program were  
2 largely preexisting tumors rather than new tumors.

3 That leaves the question of whether dapa can  
4 promote the growth of preexisting tumors. We  
5 examined evidence for tumor promotion first in our  
6 general preclinical program.

7 A hallmark of tumor promotion is tissue  
8 hyperplasia. In the chronic toxicology and  
9 carcinogenicity studies, there was no increase in  
10 bladder hyperplastic lesions even at high exposure  
11 multiples.

12 Another sign of tumor promotion is  
13 progression of hyperplastic lesions. In the  
14 carcinogenicity studies, there was no progression  
15 of background hyperplastic lesions or conversions  
16 of these lesions to tumors, with the limitation  
17 that there were a fairly small number of these  
18 lesions, particularly in the rats.

19 Tumor promotion can be driven by immunologic  
20 changes or, in the case of the bladder, by  
21 irritation. Looking at the chronic toxicology and  
22 carcinogenicity studies, there is no evidence of

1       these mechanisms at play.

2               Sex hormones are also associated with tumor  
3       promotion. The dog toxicology studies and the  
4       reproductive toxicology studies are sensitive  
5       indicators of hormonal changes. We saw no evidence  
6       in these studies for any perturbations of sex  
7       hormones.

8               To further address the question of whether  
9       dapa or urinary changes can promote the growth of  
10      preexisting bladder tumors, we carried out a series  
11      of special studies.

12              We looked at the effect of dapa on human  
13      bladder cancer cells. High concentrations of dapa  
14      had no stimulatory effect on multiple human bladder  
15      cancer cell lines in an in vitro proliferation  
16      model. And in a complimentary in vivo model, again  
17      dapa had no stimulatory effect on human bladder  
18      cancer xenografts.

19              We also looked in tissue culture at the  
20      effect of adding glucose on the growth rate of  
21      human bladder cancer cells. In multiple human  
22      bladder cancer cell lines, as glucose

1 concentrations were raised, there was no increase  
2 in growth rate; and at high concentrations, glucose  
3 actually slowed down the growth rate, exhibiting a  
4 cytostatic effect on bladder cancer cells, still at  
5 concentrations below the glucose concentration  
6 observed in the urine of treated patients.

7 We further looked at SGLT-2 knockout mice,  
8 where glucosuria is lifelong. We saw no  
9 precancerous or other histological alterations in  
10 the bladders of these animals.

11 Finally, there is a characteristic gene  
12 expression profile for tumor promoters. We did not  
13 see this typical gene expression profile in animals  
14 treated with dapa, nor did we see changes in genes  
15 associated with bladder cancer.

16 At this point, I would like to summarize the  
17 sponsor's assessment of the issue of bladder  
18 cancer. While there was no overall imbalance in  
19 malignancies, as in any clinical trial program we  
20 saw numeric imbalances in specific types of  
21 malignancies.

22 The largest individual imbalance was in

1 bladder cancer, and that became a question for us  
2 and the agency. With only 11 cases in total, you  
3 can't tell from the numbers alone whether this is a  
4 chance finding or a true indicator of bladder  
5 cancer risk. So you have to look to other sources  
6 of evidence.

7 First we looked more closely at the  
8 individual cases, and they don't suggest a causal  
9 relationship. The clinical characteristics are  
10 indicative of preexisting cancers in patients with  
11 the usual risk factors, and they were identified on  
12 study for reasons that aren't directly related to  
13 tumor growth.

14 Of course, patients receiving dapagliflozin have more  
15 urinary symptoms, so it's possible that they were  
16 worked up more aggressively, and that could create  
17 a diagnostic bias. Unfortunately, our trials were  
18 not designed to collect data on these sorts of  
19 workups, so we can't really test this hypothesis.

20 Next we looked to see whether a causal link  
21 could be biologically plausible. To do this, we  
22 conducted an extensive preclinical program

1 developed through discussions with the FDA and  
2 other experts. At very high multiples of exposure  
3 in three species of animals, we did not see changes  
4 that would indicate a causal relationship.

5 In animals, dapagliflozin did not cause bladder  
6 cancer. Dapagliflozin did not increase bladder tissue  
7 proliferation. And this is in animals that were  
8 not only exposed to high levels of dapagliflozin but also  
9 had increases in urine flow, volume, and glucose at  
10 the same time, similar to patients who get dapagliflozin.

11 You also have to consider whether there may  
12 be a mechanism at play, which could lead to a  
13 higher incidence of bladder cancer on dapagliflozin. We  
14 don't see evidence for such a mechanism. Dapagliflozin is  
15 highly specific for SGLT-2. Dapagliflozin is not genotoxic  
16 and did not cause gene expression changes  
17 characteristic of tumor promoters. And dapagliflozin did  
18 not exhibit any known tumor promoter properties  
19 such as local irritation or immunologic or hormonal  
20 changes.

21 It's also highly unlikely that dapagliflozin promotes  
22 cancer cell growth through its effect on urine

1 flow, volume, or composition. Diuretics increase  
2 urine flow and volume, and have been used for  
3 decades without any observed effect on bladder  
4 cancer incidence.

5 Glucose itself does not appear to have an  
6 effect on the growth of human bladder cancer cells,  
7 and to our knowledge, in patients, similar urine  
8 changes induced by spontaneous mutations in SGLT-2  
9 or by treatment with the SGLT-2 inhibitor  
10 canagliflozin have not been associated with an  
11 increase in the incidence of bladder cancer. So  
12 there would not appear to be any direct link to  
13 dapa's mechanism.

14 In our discussions with the agency, they  
15 have suggested to study an in situ bladder cancer  
16 model. It's been our understanding that this study  
17 could be conducted post-approval, and we're  
18 preparing for this study now.

19 Bladder cancer will also be assessed after  
20 approval in the DECLARE outcome study, which is  
21 already underway, and by monitoring bladder cancer  
22 incidence in large databases through

1       pharmacoepidemiology studies.

2               It's common for some uncertainty to remain  
3       at the end of a clinical program, especially around  
4       rare events such as in the case of dapagliflozin bladder  
5       cancer. And while we're fully committed to the  
6       additional post-approval work, it's important to  
7       recognize that the existing body of evidence, both  
8       clinical and preclinical, is extensive, well-  
9       conducted, and consistent.

10              Our conclusions, based on the data we have  
11       shown you, is that the weight of evidence, to a  
12       reasonably high degree of certainty, does not  
13       support a causal link between dapagliflozin and bladder  
14       cancer.

15              Let's move now to cardiovascular safety.  
16       Dapagliflozin affects several CV risk factors. Glucose,  
17       weight, and blood pressure move in a beneficial  
18       direction, but there's also mixed lipid changes,  
19       and there are changes in emerging risk factors like  
20       uric acid.

21              In accordance with the 2008 FDA guidance, we  
22       performed a cardiovascular meta-analysis, looking



1 at the adjudicated events across the 21 studies of  
2 the all phase 2b and 3 safety pool to assess the  
3 overall impact of data on cardiovascular risk. The  
4 meta-analysis ruled out an unacceptable increase in  
5 cardiovascular risk with dapa therapy.

6 The prespecified primary endpoint, which was  
7 agreed to with the FDA, was a composite of CV  
8 death, myocardial infarction, stroke, and  
9 hospitalization for unstable angina. The hazard  
10 ratio point estimate for the primary endpoint was  
11 0.79. The upper bound of the 95 percent confidence  
12 interval was 1.07. This is well below the 1.8  
13 margin for a program-wide meta-analysis required by  
14 the FDA guidance for approval.

15 A high CV risk subgroup, shown in blue, was  
16 predefined for the CV meta-analysis. This subgroup  
17 was predefined in order to gather the largest  
18 amount of outcome data possible from patients with  
19 known CV disease.

20 This high-risk subgroup comprised all  
21 patients with known coronary artery,  
22 cerebrovascular, or peripheral vascular disease, or

1 with heart failure. The hazard ratio point  
2 estimate for the primary endpoint for this subgroup  
3 was 0.81, with a confidence interval upper bound of  
4 1.16.

5 In the middle, the prespecified secondary  
6 endpoint was comprised of components of the primary  
7 endpoint plus hospitalization for congestive heart  
8 failure and urgent coronary revascularization.

9 The hazard ratio point estimate for the  
10 secondary endpoint, as for the primary endpoint,  
11 favored dapa both for the overall population and  
12 for the prespecified subgroup of patients with a  
13 history of cardiovascular disease.

14 At the bottom are the analyses of the  
15 composite triple endpoint of CV death, MI, and  
16 stroke. Again there is no evidence of increased  
17 cardiovascular risk.

18 The primary endpoint for the individual  
19 studies is shown here. Two of the studies, studies  
20 18 and 19, were conducted solely in patients with a  
21 history of coronary artery, cerebrovascular, or  
22 peripheral vascular disease, the same three types

1 of vascular disease that qualified patients for the  
2 prespecified high-risk subgroup of the meta-  
3 analysis. As such, studies 18 and 19 constitute an  
4 operational subset of the predefined clinical  
5 subgroup of patients with a history of CV disease.

6 There are three important things to note  
7 about these studies. First, there is no a priori  
8 reason to analyze these studies in isolation from  
9 the larger prespecified clinical subgroup. The  
10 rationale for prespecifying the subgroup was to  
11 include as many events as possible to increase the  
12 precision of the estimate, and our assessment is  
13 that this prespecified high CV risk subgroup is the  
14 most suitable population for making a risk  
15 determination.

16 Second, it is important to note that studies  
17 18 and 19 were standard phase 3 diabetes studies  
18 and not cardiovascular outcomes studies. In these  
19 studies, the conduct, the collection of events, and  
20 the adjudication of events all followed the same  
21 processes as the other studies in the program, and  
22 the primary endpoints of these studies were

1 measurements of hemoglobin A1c, weight, and blood  
2 pressure, as in the other studies across the phase  
3 3 program.

4 Third, judging by the actual CV event rates  
5 in these trials, the CV risk in these studies was  
6 similar to that of the other patients in the  
7 prespecified high CV risk subgroup.

8 At the request of FDA, a separate analysis  
9 was performed combining these two studies. The  
10 analysis was first performed in 2011 as an interim  
11 analysis while long-term extensions of the studies  
12 were still ongoing, and was submitted to FDA with  
13 the major amendments.

14 At that interim analysis, the combined  
15 studies had a hazard ratio point estimate for the  
16 primary endpoint of 1.07, for the secondary  
17 endpoint of 0.89, and for the triple endpoint at  
18 the bottom of 1.27.

19 Again at the request of FDA with the  
20 completion of these two studies, they were combined  
21 and reanalyzed as part of our NDA resubmission.  
22 The hazard ratio point estimate for the primary

1 endpoint was now 0.96, for the secondary endpoint  
2 was 0.89, and for the triple endpoint at the bottom  
3 it was 1.11.

4 There was variability between the two  
5 studies. The composite endpoints for study 18 all  
6 had hazard ratios greater than 1, and the composite  
7 endpoints for study 19 all had hazard ratios less  
8 than 1.

9 While this analysis covers only two of the  
10 21 studies in the meta-analysis, these data are  
11 consistent with the conclusion from the meta-  
12 analysis that an unacceptable increase in  
13 cardiovascular risk with dapa therapy has been  
14 ruled out.

15 In the overall population, the CV meta-  
16 analysis findings were also consistent across  
17 endpoint components. The point estimates for the  
18 hazard ratio were either neutral or favored dapa  
19 for each individual component of the primary and  
20 secondary endpoints, CV death, MI, stroke,  
21 hospitalization for unstable angina, unplanned  
22 coronary revascularization, and hospitalization for

1 heart failure.

2 The Kaplan-Meier plots show that the hazards  
3 for dapa and control were similar until around 8 to  
4 9 months, at which time the curves diverged,  
5 favoring dapa. Given that canagliflozin had an  
6 excess of cardiovascular events in the first month,  
7 the FDA in their briefing book raised the question  
8 or whether an increase in early CV events could be  
9 a class effect.

10 Shown here for the dapa program is a hazard  
11 rate for the primary endpoint by month, with dapa  
12 in orange and placebo in grey. The number of  
13 events for each month is shown at the bottom. In  
14 the first month of exposure, there were 8 primary  
15 endpoint events in the dapa group and 2 in the  
16 control group, remembering that there were nearly  
17 twice as many patients randomized to dapa as  
18 control.

19 Of note, there is no indication that these  
20 early events were related to volume depletion.  
21 None of these patients had adverse events of volume  
22 depletion or hypotension, and there is no

1 association of early timing of CV events with the  
2 risk factors for volume depletion with dapag,   
3 namely, older age, moderate renal impairment, or  
4 loop diuretic use.

5 Looking at the hazard rate, there is  
6 considerable month-to-month variability, so any  
7 individual month does not tell the whole story.  
8 The dapag hazard rate in the first month was not  
9 particularly elevated. It was typical of the dapag  
10 hazard rate throughout the program.

11 The placebo rate in the first month was  
12 lower than at most later time points in the  
13 program, and in fact was unusually low for a  
14 diabetic population. The placebo rate then rose in  
15 the second month and exceeded the dapag rate.

16 Our assessment is that the small imbalance  
17 in early events is a function of month-to-month  
18 variability in the hazard rate rather than an  
19 increase with dapag in early hazard.

20 In accordance with the FDA guidance, the CV  
21 meta-analysis of the dapag clinical program ruled  
22 out an unacceptable increase in cardiovascular

1 risk. The primary endpoint hazard ratio favored  
2 dapa, with an upper bound of the 95 percent  
3 confidence interval well below the 1.8 required by  
4 the guidance.

5 The results were consistent across the  
6 primary, secondary, and MACE composite endpoints.  
7 They were consistent across the individual endpoint  
8 components. And they were consistent across the  
9 overall population and the high-risk subgroup.

10 With respect to this last point, the FDA has  
11 asked for you to comment on the appropriate  
12 populations for assessing CV safety. We want to be  
13 clear that in our assessment, the best evidence  
14 comes from the prespecified meta-analysis of all  
15 patients from all 21 studies.

16 It's also appropriate to look at the  
17 prespecified subpopulation of patients with CV  
18 disease to help evaluate effects in higher-risk  
19 patients. An inordinate amount of weight, however,  
20 should not be placed on evidence derived from the  
21 post hoc breaking of the prespecified population  
22 into smaller subpopulations, such as studies 18



1 and 19 alone.

2 Yet even examination of these two studies  
3 still supports our conclusion that dapagliflozin is not  
4 associated with an unacceptable increase in  
5 cardiovascular risk.

6 Finally, while the data are not sufficient  
7 to conclusively rule out a class effect on early CV  
8 events, the CV hazard rate with dapagliflozin at early time  
9 points was not elevated compared to later time  
10 points.

11 Our NDA resubmission addressed the issues  
12 outlined in the FDA's complete response letter. As  
13 we've shown you, new data mitigates the concerns  
14 around liver safety, malignancy, and cardiovascular  
15 risk, and the totality of data strongly supports  
16 the approval of dapagliflozin.

17 Dr. John Wilding, professor of medicine  
18 at the University of Liverpool and a practicing  
19 diabetologist, will now provide a clinical  
20 perspective on the benefit/risk profile of dapagliflozin and  
21 how it applies to unmet medical need in patients  
22 with type 2 diabetes.

1 Dr. Wilding?

2 **Sponsor Presentation - John Wilding**

3 DR. WILDING: Thank you, and good morning.

4 My name is John Wilding. I'm a clinical  
5 endocrinologist and academic researcher based at  
6 the University of Liverpool in the United Kingdom.  
7 I served as an investigator for some of the  
8 dapagliflozin trials, and since dapagliflozin is  
9 approved in the United Kingdom, I do have  
10 experience prescribing it to my patients.

11 I am a paid consultant to the sponsor, as  
12 well as having had institutional support from the  
13 sponsor, but I have no financial interest in the  
14 outcome of this meeting.

15 The question I'm going to start with is why  
16 do we need new medicines for people with diabetes?  
17 Firstly, as we've already heard from Dr. Bays, more  
18 than half the patients attending diabetes clinics  
19 around the world do not achieve their glycemic  
20 goals. But part of this is due to limitations of  
21 the existing therapies. These can be effective,  
22 but the limitations do impact on whether the

1 patients are able or like to take the treatments.

2 The problems that impact on this include  
3 hypoglycemia, particularly with sulfonylureas and  
4 insulin; and also weight gain, which we see with  
5 sulfonylureas, insulin, and thiazolidinediones.  
6 This is particularly important because diabetes is  
7 a condition that is largely caused by obesity.

8 Gastrointestinal side effects, fluid  
9 retention, and concerns about cardiovascular safety  
10 can also impact on patients' willingness to take  
11 some of the existing glucose-lowering treatments.

12 Finally, I think it's important to remember  
13 that all of our treatments are at best limiting the  
14 natural course of the disease. They're not curing  
15 it. They're certainly not preventing progression,  
16 and so we do see progressive failure with existing  
17 medications and the need to add new medications  
18 over time.

19 So moving on to think about the SGLT-2  
20 inhibitors as a new class of drugs, and  
21 specifically dapagliflozin, I think it's important  
22 to consider the risk/benefit ratio compared to

1 other agents and also in relation to some of the  
2 uncertainties that we've been discussing today.

3 In terms of benefit, what we've seen across  
4 the board in the data that has been presented this  
5 morning is that dapagliflozin is effective at  
6 lowering blood glucose and HbA1c right across the  
7 range of the disease, from patients on monotherapy  
8 right through to those with advanced disease who  
9 are requiring treatment with insulin. And this  
10 glucose-lowering effect is at least equivalent to  
11 what we see with other agents, for example,  
12 sulfonylureas.

13 Importantly, we also see a consistent weight  
14 loss of around 2 to 3 kilograms, which is again  
15 very important for an obesity-related disease. And  
16 even in those patients treated with insulin, we see  
17 a modest degree of weight loss compared to weight  
18 gain in those patients who are treated with  
19 placebo.

20 In terms of risks, I'm going to address the  
21 problems of genital infections, urinary tract  
22 infections, and volume depletion later in my talk.

1           So from my perspective as a clinician, there  
2     are four main reasons why I think dapagliflozin is  
3     a valuable addition to our armamentarium for  
4     treating type 2 diabetes. First, diabetes is an  
5     obesity-related disease, and as well as being  
6     effective for glucose control, dapagliflozin also  
7     helps patients lose weight. And this is something  
8     that many of our patients are seeking when they're  
9     looking for treatment for their diabetes.

10           Although we do see some weight loss with  
11    other agents, such as metformin and possibly even  
12    with the DPP-4 inhibitors, the SGLT-2s are really  
13    the only oral agents that we have that can help  
14    patients lose clinically significant amounts of  
15    weight.

16           Secondly, many of our patients also have  
17    inadequate blood pressure control. Data from the  
18    United Kingdom suggests that over half the patients  
19    don't have adequate blood pressure control. And  
20    dapagliflozin can also help in that respect.

21           Thirdly, the effects of hypoglycemia are  
22    often underestimated in terms of their cost and the

1        impact that this has on patients. And there's  
2        certainly no doubt that episodes of hypoglycemia  
3        can reduce compliance. And I think it's very  
4        important to highlight that dapagliflozin has a low  
5        intrinsic risk of causing hypoglycemia in the  
6        treatment of type 2 diabetes.

7                Finally, as a clinician, I see a lot of  
8        patients who are being treated with insulin who  
9        really do have very poor control. And this is  
10       because insulin promotes weight gain. It causes  
11       hypoglycemia. And we often find that increasing  
12       the insulin dose just creates a vicious cycle of  
13       weight gain and further increases in the insulin  
14       dose.

15               In the studies that I was involved with  
16       using dapagliflozin together with insulin together  
17       with more recent clinical experience, we've shown  
18       that this agent can help break that cycle of weight  
19       gain and escalating insulin doses, improving  
20       control, stabilizing the insulin dose, and  
21       stabilizing body weight.

22               In terms of safety and tolerability, I do

1 think that dapagliflozin overall has a good  
2 profile. The genital and urinary tract infections  
3 are an issue that I'm very aware of with this class  
4 of drugs. But I do think it's important, as long  
5 as the patients and clinicians are properly advised  
6 about this issue, that it's possible to provide  
7 prompt therapy with appropriate antifungals or  
8 antibacterial agents, and this becomes more of an  
9 inconvenience than a major clinical concern.

10 I do think it's important to emphasize that  
11 although there is a numerical increase in bacterial  
12 and urinary tract infections, I'm very reassured by  
13 the fact that there's no increase in more serious  
14 events such as pyelonephritis.

15 Moving on to the issue of volume depletion,  
16 this adverse event is usually mild and only very  
17 rarely causes clinical symptoms. And although  
18 these agents do cause modest volume depletion, I  
19 think it's important to hit that we do see a  
20 similar risk with other commonly used drugs -- for  
21 example, thiazide diuretics, which are very widely  
22 used to treat hypertension and in fact probably

1       cause a greater degree of volume depletion than we  
2       see with dapagliflozin. And we don't have major  
3       concerns about using those sorts of drugs in  
4       clinical practice.

5               Again, I think if we educate patients and  
6       physicians about this adverse event and make sure  
7       the drug isn't started in volume-depleted patients,  
8       and that patients are advised to stop therapy if  
9       they develop intercurrent illnesses such as nausea  
10      and vomiting, that this risk can be managed safely.

11              We've heard a lot just now about the  
12      numerical imbalance in blood cancer. I am very  
13      reassured by the preclinical and clinical data that  
14      we've seen that really don't support a causative  
15      link between dapagliflozin and the development of  
16      bladder cancer.

17              I'm also reassured by the fact that there's  
18      a large outcomes trial and other postmarketing  
19      monitoring underway which will collect more  
20      information about this issue in the future.

21              Finally, considering cardiovascular disease  
22      risk, we do have some reassuring data, with a point



1 estimate that is below 1 in terms of the relative  
2 risk of developing cardiovascular disease in  
3 patients taking dapagliflozin. And again, we're  
4 going to get much more information in the future  
5 from the ongoing outcomes study.

6 So to summarize, effective control of  
7 hypoglycemia remains a major challenge in the  
8 treatment of patients with type 2 diabetes. SGLT-2  
9 inhibitors such as dapagliflozin can play an  
10 important role in treating this condition. It can  
11 lower blood glucose with a low risk of hypoglycemia  
12 and with beneficial effects on weight and blood  
13 pressure.

14 The adverse effects seen in clinical  
15 practice, particularly genital and urinary tract  
16 infections, are manageable with standard therapy,  
17 and I think we can reduce the risk of volume  
18 depletion by providing the right clinical advice to  
19 treating physicians and patients.

20 Thank you very much for your attention, and  
21 I'd now like to invite Dr. List to discuss the  
22 sponsor's post-approval plans.

**Sponsor Presentation - James List**

DR. LIST: Thank you, Dr. Wilding.

We have shown you today the results of our preapproval development program. We are committed to continuing monitoring of dapagliflozin safety post-approval.

Central to this effort is the DECLARE study, the largest clinical outcomes trial undertaken in a diabetes population to date. DECLARE, which started enrollment in April of this year, is a randomized, controlled trial with a planned 17,150 patients receiving either dapa or placebo.

A planned 1390 events will contribute to the primary endpoint of CV death, MI, or ischemic stroke. Patient follow-up is planned for a median of 4 and a half years, providing an estimated total exposure of approximately 77,000 patient-years.

Included in the assessments in this study are blinded adjudication of cardiovascular events, malignancies, and hepatic events. DECLARE is being followed by an expert independent data monitoring committee, who periodically review the safety data

1 coming in from the trial and the emerging  
2 risk/benefit profile.

3 The trial design also incorporates periodic  
4 predefined evaluations of bladder cancer performed  
5 by the data monitoring committee, with the accrual  
6 of every set of 8 bladder cancer events.

7 In addition to DECLARE, the post-approval  
8 risk management plan includes pharmacoepidemiology  
9 studies of cancer, acute liver injury, acute kidney  
10 injury, and severe urinary tract infections to  
11 provide real world evidence pertaining to these  
12 issues. These pharmacoepidemiology studies are  
13 ongoing in Europe, and will be expanded to include  
14 U.S. databases upon approval.

15 We are also planning to do additional  
16 preclinical tumor promoter work, as described by  
17 the FDA in their formal dispute resolution request  
18 letter as being reasonable to conduct post-  
19 approval. And we have already undertaken the  
20 preliminary work to adapt these models so they can  
21 be used to study dapagliflozin.

22 Finally, pharmacovigilance and safety

1 monitoring activities are employed in ongoing  
2 trials, and spontaneous reports of adverse events  
3 are collected from the 38 countries where dapa has  
4 already been approved.

5 So let's come back now to what you heard  
6 from Dr. Bays and Dr. Wilding. Type 2 diabetes is  
7 a progressive disorder. Over time, patients  
8 struggle to improve or even to maintain their  
9 glycemia, and they struggle to maintain control of  
10 their weight and of their blood pressure. Our data  
11 show that the risk/benefit profile of dapa is  
12 positive and warrants approval to help address this  
13 unmet medical need.

14 Ultimately, more choices are needed for  
15 treating diabetes. By utilizing the kidney's  
16 ability to excrete glucose in the urine,  
17 dapagliflozin represents an innovative new  
18 treatment option for patients and healthcare  
19 providers. Thank you, and we look forward to the  
20 discussion.

### 21 **Clarifying Questions**

22 DR. SMITH: I'd like to thank the sponsor,

1 and we do have time for some discussion. We'll  
2 start with Dr. Lewis.

3 DR. LEWIS: I have three brief questions.

4 Core slide number 119, which corresponds to  
5 figure 32, I want to be sure I understand the  
6 safety population long-term follow-up numbers.  
7 There's approximately 1500 people who have been  
8 exposed to dapa for 2 years, 234 that have been  
9 exposed for 3 years, and 176 for 4 years. Is that  
10 correct?

11 DR. LIST: That's correct.

12 DR. LEWIS: Okay. My second --

13 DR. LIST: I should say that's correct for  
14 this pool. This is 21 studies. There's actually  
15 24 in the submission. But yes.

16 DR. LEWIS: How much does that change the  
17 number, to add the other three studies? Not much?

18 DR. LIST: For the long-term, not much.

19 DR. LEWIS: Okay. My second question is  
20 could you just explain how it happened that the  
21 robust preclinical trials were not done prior to  
22 this meeting? Did they not ask you for them at

1 first, or how did that happen?

2 DR. LIST: Are you asking prior to the last  
3 advisory committee meeting?

4 DR. LEWIS: This meeting. Like their  
5 current briefing document suggests that your  
6 preclinical models are not robust enough for  
7 bladder cancer. And I guess you're thinking of  
8 going ahead and doing it. But how come it didn't  
9 happen?

10 DR. LIST: Yes. I see your question. This  
11 is a very important issue to understand, these  
12 models and what it takes to adapt them to use with  
13 dapagliflozin.

14 If the committee would allow, I would like  
15 both our internal and external preclinical experts  
16 to explain what the timeline for conducting these  
17 trials is and how it relates to dapagliflozin.  
18 Would that be possible?

19 DR. LEWIS: Sure, if it's okay with the  
20 chair.

21 DR. SMITH: Yes. That would be fine. I  
22 would just ask you to keep it as brief as possible

1       because we have quite a few questions and limited  
2       time.

3               DR. LIST:   So Drs. Reilly and Cohen?

4               DR. REILLY:  Tim Reilly, drug safety,  
5       Bristol-Myers Squibb.

6               Specific to your question, the  
7       characterization of the briefing document is  
8       perhaps an incomplete characterization of, I think,  
9       the productive dialogue we've had.

10              Initially, the initial discussions we had  
11      with the agency were around the general topic of  
12      tumor promotion, and so the studies, the special  
13      tumor promoter studies that Dr. List mentioned,  
14      were the studies that we conducted.  And I think in  
15      the briefing document the FDA now agrees that  
16      dapagliflozin is not a direct tumor promoter.

17              The additional studies that the agency  
18      referenced are studies that are not off-the-shelf  
19      studies for direct assessment of tumor promotion.  
20      SO let me speak to them specifically.

21              One is an orthotopic model, where you  
22      actually inject bladder tumor cells up into the

1 bladder. That's a model that's predominately been  
2 developed for anti-cancer drugs and looking at  
3 suppression. So there's a significant variability,  
4 and the kinetics of the model are very difficult to  
5 assess.

6 So we've been working with several external  
7 contract laboratories and academic advisors to work  
8 up the model to understand the kinetics of when the  
9 tumor actually connects and grows and when we can  
10 actually introduce treatment with dapagliflozin,  
11 and now have preliminary results to assess the pros  
12 and cons of that model.

13 The other one is a chemical-induced tumor  
14 promoter model using the chemical BBN, which is  
15 both a tumor initiator and tumor promoter. In the  
16 literature, that's a model that's complicated  
17 predominately by the fact that it's usually  
18 delivered in the drinking water. So with a  
19 molecule like dapagliflozin, which increases mass  
20 of urinary output, the control of that experiment  
21 is very difficult. It also is a model that has a  
22 very steep dose-response curve. So trying to



1 understand enhancement of tumor growth is quite  
2 difficult.

3 So we've initiated two sets of study in rats  
4 and in mice to understand the dose-response curve  
5 to understand the kinetics, and those are  
6 relatively long models. The two studies we did are  
7 both 24 weeks of in-life duration as well as the  
8 follow-up.

9 So going back a year to when that initial  
10 discussion happened, we've spent that year trying  
11 to work up these models to now have a productive  
12 discussion with the FDA.

13 I invite Dr. Cohen to comment on the models  
14 themselves.

15 DR. COHEN: My name is Dr. Sam Cohen. I'm  
16 from the University of Nebraska Medical Center,  
17 department of pathology and microbiology. I'm a  
18 paid consultant. I have no financial interest in  
19 the outcome of this deliberation.

20 I'm a practicing surgical pathologist  
21 subspecializing in urologic pathology, and I've  
22 also been involved with animal models and

1 mechanisms of carcinogenesis for nearly 50 years,  
2 since I was an undergraduate at the University of  
3 Wisconsin.

4 I've worked with both of these models, and  
5 there's difficulties with both of them. And to be  
6 honest, my own interpretation of the data is, you  
7 already have the results that you can anticipate  
8 from these models.

9 First of all, let me deal with the  
10 orthostatic model. This is a very difficult model  
11 to standardize. Basically, it was developed at NCI  
12 originally for the screening of cancer chemotherapy  
13 agents, particularly intravesical assessments.

14 You have to produce this by -- you can't  
15 just instill the tumor cells into the bladder and  
16 expect them to take. You have to first damage the  
17 bladder surface, and then you instill the bladder  
18 cells and then they grow.

19 The problem is, the process of damaging the  
20 bladder surface and the installation of the cells  
21 and the growth of the cells gives you a lot of  
22 variability in the results, so that you really

1       can't get an easily detectable signal, particularly  
2       for something that might be as subtle as you would  
3       see with dapagliflozin.

4               The other issue is the issue of the BBN  
5       model. I was the first one to actually develop a  
6       two-stage model of carcinogenesis for the bladder,  
7       now almost 35 years ago. And I also worked with  
8       Dr. Ito in Japan as a visiting professor, who is  
9       the one that actually developed the BBN model  
10      itself. BBN is a nitrosamine that's bladder-  
11      specific for a number of tissues.

12             The BBN two-stage model is only useful in  
13      the rat. It can't be used in the mouse or the dog  
14      or other species. It's rat-specific. And for that  
15      matter, it's only been standardized in the male  
16      rat; it doesn't work very well in a female rat,  
17      which causes a problem.

18             The difficulty you have in interpreting the  
19      results of the BBN model in general is that the  
20      characteristic finding of tumor promoters per se is  
21      that they increase cell proliferation. And what we  
22      know from studying a huge number of chemicals in

1       this model, as well as other two-stage models in  
2       the bladder, is that any agent that's positive in  
3       these models will produce increased cell  
4       proliferation of the bladder by itself without  
5       prior treatment of BBN. And you don't see that  
6       with dapagliflozin.

7               So just by the fact that that was negative  
8       in the short-term and long-term study for an  
9       increase in proliferation, whether tumors or  
10      hyperplasia, tells you that it's going to be  
11      negative in the BBN model. Likewise, anything that  
12      increases cell proliferation in the bladder in the  
13      rat will be positive in the BBN model.

14             So it ends up that it's not predictive of  
15      human carcinogenesis at all. For example, things  
16      that are positive in the BBN model include things  
17      like saccharine, vitamin C, sodium chloride, sodium  
18      bicarbonate, MSG. And the other is that things  
19      that are negative for hyperplasia in the bladder in  
20      the rat are negative in the been model.

21             Furthermore, I think you already have some  
22      evidence. The concern is that it's dapagliflozin

1 plus glucosuria that's causing the proliferation of  
2 these tumor cells.

3 Clearly dapa by itself, based on the in  
4 vitro studies, is not increasing cell proliferation  
5 of these tumors, and as Dr. Bajorin pointed out,  
6 the patients who are developing the bladder tumors  
7 in these clinical trials are behaving just like you  
8 would expect a bladder tumor patient to be  
9 behaving, whether they have the drug or not. The  
10 course over time is very similar.

11 The other issue is that even though there  
12 was no increase in hyperplasia in a 2-year or in  
13 short-term studies, there is a background incidence  
14 of hyperplasia in the rat studies, and you don't  
15 see any progression of these lesions to tumors in  
16 the 2-year bioassay. So I think the evidence  
17 really is very strong and I think very convincing.

18 DR. LEWIS: Thank you. I think the answer  
19 to my question is that you feel that the  
20 preponderance of preclinical studies you did  
21 appropriately answer the question of  
22 carcinogenicity both for the drug and glucosuria,

1 the environment.

2 When the FDA asked you to do these other  
3 preclinical studies, which you think are arguably  
4 complex and not necessarily easy to do or maybe  
5 even additional information, you initiated them.  
6 Is that right?

7 DR. COHEN: I think the company has been  
8 initiating them --

9 DR. LEWIS: Great. That's great. That's  
10 what I needed to know.

11 DR. COHEN: -- and is trying to develop an  
12 appropriate method that could be used --

13 DR. SMITH: Okay. And I think we're going  
14 to move along now because we want to get some more  
15 questions.

16 Dr. Thomas?

17 DR. THOMAS: Just a quick question. Do you  
18 know what the prevalence of hematuria is when  
19 subjects enter the study and what the incidence is  
20 during the course of follow-up? I may have missed  
21 it in the briefing documents.

22 DR. LIST: It was a little hard to hear you.

1 The incidence of hematuria at baseline and  
2 follow-up? Was that your question?

3 DR. THOMAS: The prevalence at enrollment  
4 and then, over time, what the incidence was.

5 DR. LIST: Yes. We have some data that we  
6 can share with you on that.

7 Can we have the slide on hematuria at  
8 baseline and on study, please?

9 While that's coming up, roughly about  
10 15 percent of patients at baseline had hematuria.  
11 It was, I believe, a little bit larger on study  
12 with the multiple determinations that took place on  
13 study, and relatively balanced between  
14 dapagliflozin and control, a little bit higher on  
15 dapagliflozin.

16 Slide 34-23, please. So the top row here is  
17 patients having at least one positive dipstick  
18 prior to receiving the study drug. So that's  
19 either at the randomization visit or the screening  
20 visit, typically.

21 Then the following row is at any time during  
22 study. And so you see these percents increasing,

1 but remembering that people are getting tested a  
2 lot more over the course of the study.

3 DR. THOMAS: Just a quick follow-up. How  
4 does that compare to any other data in a general  
5 population of people followed up with diabetes? Is  
6 that comparable? I know there might be an issue  
7 because you were actually looking for this, where  
8 you might actually find more cases.

9 DR. LIST: Yes. We did in fact test for  
10 hematuria in every patient at every visit. So  
11 there was quite intensive testing.

12 I don't know if Dr. Bajorin has a sense for  
13 what the incidence of a screening population for  
14 hematuria is. If there's 15 percent of trace or  
15 greater, it jibes with Messing's data?

16 DR. BAJORIN: It's very difficult to draw an  
17 analogy. The Messing data is actually men over 50  
18 and not the general population, and it wasn't  
19 screened for diabetics. So it's really hard to  
20 compare the two populations.

21 DR. LEWIS: I think that in studies of  
22 diabetics who had urinalysis, I think 8 percent or



1       10 percent sounds like what is seen in many studies  
2       that did UAs at the beginning.

3               DR. SMITH: Dr. Brittain, you have a  
4       question?

5               DR. BRITTAIN: Okay. Actually, I was  
6       interested in the same question that Dr. Thomas  
7       had, but I think a little further, which is looking  
8       at the subgroup with hematuria or pre-cancer,  
9       however you want to define it, so then what is the  
10      rate in the two groups, in the dapa group and the  
11      control group in that subgroup, of bladder cancer?

12              DR. LIST: We have not done that analysis,  
13      looking at the rate within those subgroups.

14              DR. BRITTAIN: Then on slide 78, just to  
15      confirm, are all these rate ratios done as a meta-  
16      analysis as opposed to just lumping? Because it  
17      looks on some of your slides you're just lumping  
18      these studies together. And some of them have  
19      different allocation schemes, and it's problematic  
20      to just lump them.

21              DR. LIST: Yes. I'd like to ask Dr. Henry  
22      to address the methodology, statistical

1 methodology, here.

2 DR. HENRY: David Henry, Bristol-Myers  
3 Squibb, biostatistics.

4 For these studies, we do indeed stratify by  
5 study. You mentioned there were other places where  
6 it looked as if we were just combining all the data  
7 without it in those presentations in some other  
8 places. Not in CV; CV we stratify. Cancer we  
9 stratify. Anywhere there's a confidence interval,  
10 we stratify.

11 There's a few other places where we give raw  
12 rates. But we've also looked at it with  
13 stratification, and we see results that are similar  
14 to what we see here.

15 DR. BRITTAIN: One quick other question. In  
16 the cardiovascular analyses, are you showing a mix  
17 of studies that are compared to placebo -- and I'm  
18 including add-on studies in that context as  
19 well -- and the studies that are comparing dapa to  
20 an active control?

21 DR. LIST: Yes. Our primary analysis looks  
22 at all studies, stratified by study. But it

1 includes the active control studies, of which there  
2 are three. Two are with metformin as an active  
3 control, and one with glipizide as an active  
4 control.

5 DR. BRITTAIN: So did you ever do it just  
6 looking at the studies that are placebo?

7 DR. LIST: We have done sensitivity analyses  
8 looking against placebo, high dose, for example,  
9 against placebo. Would you like to see some of  
10 those results?

11 DR. BRITTAIN: If you can do it really  
12 quickly.

13 DR. LIST: Yes. Let's see. Of course,  
14 while they're pulling this up, this leads to a  
15 smaller number of patients.

16 I need versus placebo, placebo-controlled  
17 analyses of cardiovascular events. If we can't  
18 find it quickly, I can certainly come back after  
19 the break and show it to you.

20 DR. SMITH: That's what we'll plan --

21 DR. LIST: Oh, I'm sorry. We have it now,  
22 if that's okay.

1           So slide 46-4, please. Here are point  
2       estimates by dose for dapa against placebo for the  
3       primary endpoint, secondary endpoint, and the MACE  
4       triple endpoint, the dose 10 milligrams at the top,  
5       5 milligrams in the middle, and 2.5 at the bottom.

6           DR. SMITH: Okay. We need to move the  
7       schedule along. We'll have lots of time later for  
8       more questions directed to the sponsor. I would  
9       like to ask the members of the advisory committee  
10      if anyone -- there are a number who had questions.

11           If anyone is looking for some data that  
12      might need some assembly that could then be brought  
13      later today -- okay. I'm going to ask then for  
14      your comments, so Dr. Packer, and then we'll come  
15      over here.

16           DR. PACKER: Just to make sure, I just have  
17      a series of questions on the cardiovascular meta-  
18      analysis.

19           DR. SMITH: If we just focus on what might  
20      need more data, and then we're going to come back  
21      to those later, just to keep us on schedule, just  
22      so they have time to do some work if they need to.

1 DR. PACKER: Can you tell me how many  
2 patients of the patients randomized in your  
3 placebo-controlled trials had a complete follow-up  
4 for the planned duration of the study?

5 DR. LIST: Dr. Henry can address that.

6 DR. PACKER: Because the most important  
7 question is, I'm sure not everyone who was  
8 randomized actually completed the study.

9 DR. LIST: That is correct.

10 DR. PACKER: So what I would be interested  
11 in is how many people didn't complete follow-up,  
12 what you did to assess the influence of those  
13 individuals, what sensitivity analyses you  
14 included. These are all related to -- and whether  
15 you did those sensitivity analyses across all of  
16 the endpoints that you created, and whether you  
17 actually did that for the trials that were of  
18 particularly long duration.

19 So the goal here is to understand what  
20 censoring may have done to make your results look  
21 more neutral than they normally would be.

22 DR. SMITH: So again, for the sake of time,

1       what I would ask if that if you may prepare and  
2       organize the information you need for that, and  
3       then we'll come back to that this afternoon for  
4       certain.   Okay?

5               DR. LIST:   Okay.

6               DR. SMITH:   Similarly, Dr. Wilson, just if  
7       there's some data that you would like to see that  
8       might take time to pull together.

9               DR. W. WILSON:   I think the diagnostic  
10       imbalance for the bladder cancer is key.   I don't  
11       know if you got this data, but did you collect data  
12       on how many patients got scoped in one group versus  
13       the other in this large thing?   I'm just asking, if  
14       you have that data, please get it for us, not now.

15               My second question is, no one has discussed  
16       the effect of the changes in the microbiome in  
17       patients that have higher levels of glucose.  
18       Everything has been focused on glucose.

19               So have you done any colony cultures,  
20       looking at differences in the fungal microbiome,  
21       look at difference in bacteria between the patients  
22       on dapa and those off dapa?   And did you look at

1 inflammation differences among those patients that  
2 got scoped and biopsied?

3 DR. SMITH: So again, we're going to defer  
4 that and ask you to come back, and we'll address  
5 that again for certain this afternoon.

6 At this point we're going to take a short  
7 10-minute break. Committee members, please  
8 remember there should be no discussion of the  
9 meeting topic during the break amongst yourselves  
10 or with any member of the audience. And I now have  
11 10:23. We're going to resume at 10:33, in  
12 10 minutes. Thank you.

13 (Whereupon, a brief recess was taken.)

14 DR. SMITH: May I ask everybody to take  
15 their seats? We would like to start.

16 We would like to now proceed with the  
17 presentations from the FDA.

18 **FDA Presentation - Eugenio Andraca-Carrera**

19 DR. ANDRACA-CARRERA: Good morning. My name  
20 is Eugenio Andraca-Carrera. I'm a statistical  
21 reviewer in the Office of Biostatistics at CDER,  
22 and today I will discuss the cardiovascular safety

1 of dapagliflozin evaluated through a meta-analysis  
2 of randomized clinical trials.

3 Here is the outline of my presentation. I  
4 will discuss the cardiovascular of dapagliflozin  
5 analyzed at three points in time. First, I will  
6 summarize the data available at the advisory  
7 committee meeting held in July of 2011. Second, I  
8 will discuss the analysis conducted as part of the  
9 major amendment of October 2011, which is 3 months  
10 after the advisory committee meeting. And third, I  
11 will discuss the full data available today.

12 Following this discussion, I will describe  
13 the statistical methods used in the analysis of the  
14 current submission, and I will discuss the results  
15 of this analysis. Finally, I will present you a  
16 brief summary of the findings.

17 So without further delay, I will address the  
18 first topic, which is the 2011 advisory committee  
19 meeting.

20 For the July 2011 advisory committee  
21 meeting, the cardiovascular safety of dapagliflozin  
22 was evaluated through a meta-analysis of 14 phase 2



1 and phase 3 clinical trials. The prespecified  
2 endpoint of the meta-analysis was a composite of  
3 four types of events: cardiovascular death,  
4 myocardial infarction, stroke, and hospitalization  
5 for unstable angina.

6 This meta-analysis included 4,287 subjects  
7 randomized to dapagliflozin and 1,841 subjects  
8 randomized to comparators. There were a total of  
9 over 6,000 patient-years of follow-up and 78  
10 primary events, 48 on dapagliflozin and 30 on  
11 comparators.

12 At the time of the July 2011 advisory  
13 committee meeting, the estimated hazard ratio for  
14 the primary composite endpoint associated with  
15 dapagliflozin was 0.67, with a 98 percent  
16 confidence interval ranging from 0.38 to 1.18.

17 This 98 percent confidence interval was  
18 prespecified instead of a 95 percent interval as  
19 part of a two-part sequential testing strategy.  
20 And at that point, the interval successfully ruled  
21 out a risk margin of 1.8.

22 This next plot is taken from the slides

1 presented at the 2011 advisory committee meeting.  
2 It shows a forest plot of the hazard ratio of the  
3 primary endpoint in the 14 trials presented at the  
4 time of the meeting. The plot shows no evidence of  
5 increased cardiovascular risk associated with  
6 dapagliflozin at that time.

7 Now I will talk about the analysis conducted  
8 as part of the major amendment of October 2011,  
9 which included additional information.

10 In October of 2011, additional data from  
11 several ongoing randomized trials was submitted to  
12 the agency. And updated meta-analysis was  
13 conducted that included five additional trials,  
14 bringing the total number of trials to 19.

15 This major amendment included 39 percent  
16 more subjects and 43 percent more patient-years  
17 than the analysis presented at the advisory  
18 committee meeting. The major amendment included 34  
19 additional events on dapagliflozin, bringing the  
20 total number to 82, and 33 additional events in  
21 comparators, bringing the total to 63.

22 Based on this updated data, the

1 corresponding estimated hazard ratio for the  
2 primary event was 0.82, with a 95 percent  
3 confidence interval ranging from 0.58 to 1.15.  
4 Note that this point estimate was slightly higher  
5 than the 0.67 presented at the advisory committee  
6 meeting. However, the upper bound of the 95  
7 percent confidence interval still excluded the 1.8  
8 risk margin.

9 At this point I would like to pay special  
10 attention to two of the five trials included in the  
11 2011 major amendment. These two trials are  
12 especially interesting because they enrolled a  
13 population with high cardiovascular baseline risk.  
14 I will describe these two trials in the next two  
15 slides.

16 The two trials of interest will be referred  
17 as trials 18 and 19, and some key features of their  
18 design are shown on this slide. The total planned  
19 duration for these trials was 104 weeks. Trials 18  
20 and 19 were double-blinded, and they randomized  
21 subjects with a background standard of care on a  
22 1 to 1 ratio to either dapagliflozin 10 milligrams

1       daily or placebo. Each trial planned to randomize  
2       a total of approximately 900 subjects.

3               But what sets these trials apart from the  
4       other trials in the dapagliflozin development  
5       program is their inclusion criteria. As has been  
6       discussed earlier, trials 18 and 19 enrolled  
7       subjects with a prior history of cardiovascular  
8       disease, defined as any of the conditions listed at  
9       the bottom of the slide. These conditions include  
10      a history of myocardial infarction, congestive  
11      heart failure, and many others.

12              Because trials 18 and 19 enrolled a  
13      population with higher baseline cardiovascular  
14      risk, they had a larger sample size and longer  
15      follow-up than most of the other trials, the agency  
16      requested that separate analysis of cardiovascular  
17      risk be conducted in these trials alone, which I  
18      will discuss on the next slide.

19              In 2011, trials 18 and 19 had not yet been  
20      completed, so the submission at that time included  
21      data from at least 31 weeks and, at most, 76 weeks  
22      of follow-up for subjects. Note that the full

1 prespecified ratio of these trials was 104 weeks.

2           So based on the partial data from 2011, this  
3 table shows the estimated hazard ratio for the  
4 primary composite endpoint of cardiovascular death,  
5 myocardial infarction, stroke, and hospitalization  
6 for unstable angina.

7           The estimated hazard ratio was 1.07, with a  
8 95 percent confidence interval ranging from 0.64 to  
9 1.77. The table also shows estimated hazard ratios  
10 for MACE, which is defined as a composite of  
11 cardiovascular death, myocardial infarction, and  
12 stroke.

13           The partial data of trials 18 and 19 shows a  
14 non-statistically significant imbalance of MACE.  
15 There were 24 MACE observed among subjects  
16 randomized to dapagliflozin and 19 MACE among  
17 subjects randomized to placebo. The corresponding  
18 estimated hazard ratio for MACE was 1.27, with a  
19 95 percent confidence interval ranging from 0.69 to  
20 2.31.

21           This information was available at the time  
22 that the agency made a regulatory decision to not

1 approve this product in 2012, and the decision was  
2 based on the totality of the data available at that  
3 time, which included both benefit and risk.

4 Finally, I will discuss the data available  
5 today, which will be used to conduct an updated  
6 meta-analysis and will be the focus of the rest of  
7 my presentation.

8 The rightmost column of this table shows the  
9 data available today. There are two additional  
10 trials available today that were not included in  
11 the major amendment of 2011, bringing the total  
12 number of trials to 21.

13 The 2013 meta-analysis included only  
14 8 percent more subjects than the major amendment,  
15 but it included 18 percent more patient-years. The  
16 total number of events in the 2013 meta-analysis is  
17 178, 97 on dapagliflozin and 81 on comparators,  
18 which represents 33 more total events than the 2011  
19 major amendment. I will discuss the updated  
20 analysis using this data in more detail later.

21 As a reference, here is a list of the 21  
22 trials in the 2013 meta-analysis. The table

1 includes the trial name, duration, and sample size  
2 by treatment group. Trials 18 and 19 are  
3 highlighted and bolded at the bottom of the table.  
4 The complete data from these two trials, including  
5 the 104 weeks of follow-up, is available for the  
6 2013 submission.

7 All 21 trials on this table had been  
8 completed at the time of the submission except for  
9 trial 04, presented here in bold font. Trial 04  
10 was completed in January 2013, but the data cutoff  
11 date for the submission was November 15, 2012. So  
12 only the last two months of trial 04 were not  
13 included in the present meta-analysis.

14 Having described the trial database, in the  
15 following section I will describe the statistical  
16 methodology used in the meta-analysis. I will  
17 describe the prespecified analysis, the analysis  
18 population, endpoints, and post hoc analysis.

19 The prespecified objective of the meta-  
20 analysis was to rule out a hazard ratio of  
21 cardiovascular risk greater than 1.8 associated  
22 with dapagliflozin using the upper bound of a

1 nominal 95 percent confidence interval. This is in  
2 accordance with the 2008 FDA guidance to evaluate  
3 the cardiovascular risk of oral antidiabetic drugs.

4 The primary analysis population of the meta-  
5 analysis includes subjects randomized in the  
6 21 trials I described earlier, which includes  
7 trials 18 and 19. The secondary analysis  
8 population consists of the two trials of special  
9 interest, trials 18 and 19 alone. All analyses  
10 compared all doses of dapagliflozin pooled against  
11 all pooled comparators.

12 The prespecified primary endpoint of the  
13 meta-analysis is the same as the one presented at  
14 the 2011 advisory committee meeting, which is a  
15 composite of cardiovascular death, myocardial  
16 infarction, stroke, and hospitalization for  
17 unstable angina.

18 Now I will also presents for two secondary  
19 endpoints, the secondary endpoint that is similar  
20 to the primary but also includes unplanned coronary  
21 revascularization and hospitalization for heart  
22 failure, and the secondary endpoint of MACE, which



1 is a composite of cardiovascular death, myocardial  
2 infarction, and stroke.

3 I want to note that the agency specifically  
4 requested that the sponsors include an analysis of  
5 MACE in all updated meta-analysis of cardiovascular  
6 safety.

7 The primary analysis estimates the hazard  
8 ratio of events through a Cox proportional hazards  
9 model stratified by trial, and the model includes a  
10 term for treatment that does not include other  
11 covariates.

12 Also, we conducted sensitivity analysis,  
13 including estimated Mantel-Haenszel incidence rate  
14 ratio and a random effects incidence rate ratio,  
15 but the results were very similar to the primary  
16 analysis and therefore will not be shown in this  
17 presentation.

18 Finally, we conducted a post hoc analysis of  
19 the cardiovascular risk of dapagliflozin within the  
20 first 30 days after randomization in the 21 trials.  
21 I will discuss the rationale and results of this  
22 analysis at a later time.

1           Now I will discuss the results of the  
2       prespecified analysis.

3           This table shows a list of the 21 trials  
4       included in the meta-analysis sorted by the number  
5       of primary events. At the top of the table we have  
6       the trials with the largest number of events, and  
7       at the bottom we have trials with few or no events.

8           Trials 18 and 19 are highlighted at the top  
9       to show that they had the largest number of events  
10      observed in the dapagliflozin program; 44 percent  
11      of the total events among subjects to dapagliflozin  
12      and 54 percent of the total events in comparators  
13      were observed in trials 18 and 19.

14          This table shows results of the prespecified  
15      meta-analysis for the primary endpoint of  
16      cardiovascular death, myocardial infarction,  
17      stroke, and hospitalization for unstable angina.  
18      There were 97 events observed on dapagliflozin and  
19      81 events observed among comparators in the  
20      21 trials.

21          The estimated hazard ratio for the primary  
22      endpoint was 0.81, with 95 percent confidence

1 interval of 0.59 to 1.01 -- I'm sorry, to 1.09.  
2 The estimated hazard ratio for the secondary  
3 composite endpoint was 0.76, with 95 percent  
4 confidence interval ranging from 0.59 to 1.0. This  
5 endpoint included unplanned coronary  
6 revascularization and hospitalization for heart  
7 failure.

8 At the bottom of the table is the estimated  
9 hazard ratio for MACE in the meta-analysis. The  
10 estimate was 0.78, with 95 percent confidence  
11 interval of 0.55 to 1.11. And you can see that the  
12 estimated hazard ratios for these three endpoints  
13 were consistent.

14 The forest plot in this slide shows  
15 estimated hazard ratios for the four individual  
16 components of the primary endpoint in the meta-  
17 analysis. The plot shows that the estimated hazard  
18 ratios for cardiovascular death, myocardial  
19 infarction, stroke, and hospitalization for  
20 unstable angina are consistent, and they show no  
21 evidence of increased cardiovascular associated  
22 with dapagliflozin in the 21 trials.

1           Now I would like to discuss the  
2       cardiovascular safety of dapagliflozin, evaluated  
3       using the complete data from trials 18 and 19. But  
4       before I do that, I would like to pause to show you  
5       the baseline cardiovascular risk factors in  
6       trials 18 and 19 compared to the other trials in  
7       the meta-analysis.

8           We know, by design, that subjects in  
9       trials 18 and 19 had a higher baseline  
10      cardiovascular risk. Starting from the top,  
11      subjects in trials 18 and 19 were more likely to  
12      have a history of cardiovascular disease, to be  
13      hypertensive, to have a history of dyslipidemia and  
14      congestive heart failure.

15           They were also more likely to be smokers and  
16      to have had diabetes for longer than 10 years.  
17      They were more likely to have baseline eGFR lower  
18      than 60 milliliters per minute. And this table  
19      shows again why the agency had a special interest  
20      in analyzing these two trials separately, since  
21      they involved a population with high baseline  
22      cardiovascular risk.

1           The estimated hazard ratio for the primary  
2       endpoint in trials 18 and 19 is shown in this  
3       slide. A total of 87 subjects with an event were  
4       observed, 43 among subjects randomized to  
5       dapagliflozin and 44 on placebo. The corresponding  
6       hazard ratio for the primary endpoint was 0.98,  
7       with 95 percent confidence interval of 0.64 to  
8       1.49.

9           The second row of the table shows the  
10      estimated hazard ratio for the secondary endpoint,  
11      including unplanned coronary revascularization and  
12      hospitalization for heart failure. The estimated  
13      hazard ratio was 0.89, with the confidence interval  
14      that is shown here.

15          Finally, the last row of the table shows the  
16      estimated hazard ratio of MACE based on the  
17      complete data from trials 18 and 19. There were  
18      32 MACE observed on dapagliflozin and 29 MACE  
19      observed on placebo.

20          The estimated hazard ratio of MACE is 1.11,  
21      with a 95 percent confidence interval ranging from  
22      0.67 to 1.83. And note that the estimated hazard

1 ratio of 1.11 is smaller than the 1.27 estimated at  
2 the time of the major amendment of 2011.

3 The Kaplan-Meier plot for the primary  
4 endpoint in the pooled trials 18 and 19 is shown  
5 here, and you can see that the two survival curves  
6 cross at several points through time. The p-value  
7 for the log rank test comparing these two curves is  
8 0.92, and shows no evidence to suggest that the  
9 survival curves for dapagliflozin and placebo for  
10 the primary endpoint are different in these trials.

11 The forest plot shows the estimated hazard  
12 ratios for the four components of the primary  
13 endpoint in trials 18 and 19. If you look at the  
14 third and fourth rows from the top, there were two  
15 more strokes observed among subjects randomized to  
16 dapagliflozin and placebo. So there were three  
17 more hospitalizations for unstable angina observed  
18 among subjects on placebo. Overall, there were no  
19 meaningful differences in the risks of the four  
20 endpoints between dapagliflozin and the placebo  
21 treatment groups.

22 Finally, I would like to talk about a

1 post hoc analysis of the cardiovascular risk of  
2 dapagliflozin within the first 30 days after  
3 randomization.

4 This post hoc analysis was motivated by our  
5 experience with dapagliflozin, which is the only  
6 SGLT-2 inhibitor currently approved in the United  
7 States. The data on this slide was presented at  
8 the advisory committee for canagliflozin held in  
9 January of 2013.

10 The canagliflozin program included one  
11 dedicated cardiovascular outcomes trial, called  
12 CANVAS. The trial enrolled subjects with high  
13 baseline cardiovascular risk, and evaluated  
14 cardiovascular risk through a MACE-plus endpoint.

15 Within the first 30 days of CANVAS, an  
16 imbalance of MACE-plus events was observed, with  
17 13 events observed on canagliflozin and one event  
18 observed on placebo, which corresponds to  
19 approximately a 6.5 ratio of observed events within  
20 the first 30 days in CANVAS.

21 However, during the full duration of CANVAS  
22 and in the rest of the canagliflozin program, there

1 was no evidence of increased cardiovascular risk,  
2 as shown by the two estimated hazard ratios at the  
3 bottom of the slide.

4 The imbalance of cardiovascular risk  
5 observed in CANVAS motivated us to pay special  
6 attention to the first 30 days after randomization  
7 in dapagliflozin. In the next slide I will show  
8 you a list of the cardiovascular events observed  
9 within the first 30 days of the dapagliflozin  
10 program.

11 Here's a table that shows the primary  
12 composite events observed within the first 30 days  
13 of dapagliflozin. There were a total of 8 events,  
14 shown in the shaded rows of this table, observed  
15 among 5,936 subjects randomized to dapagliflozin,  
16 and 2 events observed among 3,403 subjects  
17 randomized to comparators. Note that 4 of the  
18 events observed in dapagliflozin occurred within a  
19 week of randomization.

20 However, if we also include secondary  
21 events, we find two additional subjects with  
22 hospitalization for heart failure in the comparator



1 arm of these trials, and none on dapagliflozin.

2 So within the first 30 days, 0.13 percent of  
3 the subjects randomized to dapagliflozin  
4 experienced a primary event compared to 0.06 of  
5 the subjects randomized to comparators. The  
6 corresponding hazard ratio for the primary event  
7 within the first 30 days is 2.77, with a very wide  
8 95 percent confidence interval, as shown here.

9 Note that there were two additional  
10 secondary events in the comparator and none on the  
11 dapagliflozin arm. So if we consider secondary  
12 events, the rates within the first 30 days are  
13 similar between both treatment arms.

14 Due to the small number of events within the  
15 first 30 days of randomization in the dapagliflozin  
16 and canagliflozin programs, it is difficult to  
17 determine whether these imbalances were caused by a  
18 class effect or whether they are a chance finding.

19 Finally, I will summarize this presentation.

20 This table shows the estimated hazard ratio  
21 for the primary endpoint of MACE in the overall  
22 meta-analysis at the three points in time I

1 discussed at the beginning of my presentation.

2 The estimated hazard ratio for the primary  
3 endpoint presented at the 2011 advisory committee  
4 meeting was 0.67. The estimated hazard ratio  
5 increased to 0.82 and to 0.81 during the next two  
6 analyses with additional trial data.

7 MACE was not presented at the 2011 advisory  
8 committee meeting, but at later time points its  
9 estimated hazard ratio was 0.79, based on the 2011  
10 major amendment, and 0.78 in the current meta-  
11 analysis. Overall, the results of this meta-  
12 analysis are consistent and show no evidence of  
13 increased cardiovascular risk associated with  
14 dapagliflozin in the set of 21 trials.

15 This table similarly summarizes the  
16 estimated hazard ratios in the population of  
17 trials 18 and 19 only. The data on these trials  
18 was not available at the time of the 2011 advisory  
19 committee meeting, so the first column of this  
20 table has been left blank.

21 From the time of the 2011 major amendment to  
22 now, the estimated hazard ratio for the primary

1 endpoint in these two trials has decreased from  
2 1.07 to 0.98, and the estimated hazard ratio of  
3 MACE has increased from 1.27 to 1.11.

4 In summary, our analysis found the  
5 following. We found no evidence of increased  
6 cardiovascular risk in the prespecified analysis.  
7 Secondary analysis and analysis of individual  
8 components of the primary endpoint were consistent  
9 and showed no evidence of increased cardiovascular  
10 risk.

11 Finally, we described a small imbalance of  
12 cardiovascular events associated with dapagliflozin  
13 observed within the first 30 days of randomization,  
14 which was similar to an imbalance observed in the  
15 canagliflozin cardiovascular outcomes trial.  
16 However, it is not possible to determine whether  
17 this imbalance may have been caused by use of  
18 dapagliflozin or whether it is a chance finding.

19 Thank you very much. That is the end of my  
20 presentation.

21 **FDA Presentation - Frank Pucino**

22 DR. PUCINO: Good morning, Mr. Chairman,

1 members of the committee, ladies and gentlemen. My  
2 name is Frank Pucino, and I'm a clinical reviewer  
3 in the Division of Metabolism and Endocrinology  
4 Products. My presentation will address the  
5 clinical efficacy and non-cardiovascular safety of  
6 dapagliflozin.

7 After a brief introduction, I will review  
8 some efficacy data, focusing in on the information  
9 that is new since the last review. I will then  
10 address some of the major non-cardiovascular safety  
11 issues, including an update on bladder cancer and  
12 hepatic safety, which were identified as major  
13 safety concerns during the first review cycle.

14 I will then discuss other adverse events of  
15 special interest, including some that are common to  
16 the SGLT-2 inhibitor pharmacologic class. And I  
17 will conclude with a summary.

18 As discussed in the previous presentations,  
19 dapagliflozin is an SGLT-2 inhibitor that inhibits  
20 renal tubular reabsorption of glucose, resulting in  
21 increased urinary glucose excretion. The effect is  
22 dependent on both plasma glucose concentration and

1 renal function.

2 The applicant is seeking approval of  
3 dapagliflozin as an adjunct to diet and exercise to  
4 improve glycemic control in adults with type 2  
5 diabetes. The proposed dose is 5 or 10 milligrams  
6 taken once daily. The applicant considers the  
7 5-milligram dose to be the appropriate dose for  
8 patients at risk for volume depletion, and does not  
9 recommend that dapagliflozin be used in patients  
10 with moderate to severe renal dysfunction.

11 The pharmacokinetics and pharmacodynamics of  
12 dapagliflozin are summarized in this slide. Key  
13 points include the following.

14 The elimination half-life is approximately  
15 13 hours, with 75 percent of an oral dose  
16 eliminated renally, primarily as a glucuronide  
17 metabolite. The upper end of the dose-response  
18 curve for glucosuria appears to be at 10  
19 milligrams. And it appears that dose adjustment is  
20 not necessary for such factors as age, gender,  
21 hepatic function, co-administered drugs, or food  
22 intake.

1           Regarding dose selection, doses from 2.5 to  
2   50 milligrams were evaluated in 12-week dose-  
3   ranging trial. In this slide, the bar chart  
4   depicts percent reduction in hemoglobin A1c, with  
5   the leftmost bar representing placebo and the other  
6   bars depicting ascending doses of dapagliflozin.

7           The fourth bar from the left represents the  
8   10-milligram dose. Looking to the right of that  
9   bar, you can see that additional hemoglobin A1c  
10   lowering was not achieved with doses greater than  
11   10 milligrams. However, genitourinary infections  
12   and laboratory abnormalities, such as  
13   hyperphosphatemia and increases in hematocrit,  
14   were more common in the 20- and 50-milligram  
15   dapagliflozin treatment arms.

16           The majority of efficacy data for  
17   dapagliflozin were presented at the first EMDAC  
18   meeting in July of 2011. This portion of the  
19   presentation summarizes overall efficacy findings  
20   of the product, including new efficacy data from  
21   three additional phase 3 clinical trials, one  
22   evaluating the efficacy of dapagliflozin as add-on

1 to sitagliptin and two in type 2 diabetes patients  
2 with hypertension.

3 You just heard cardiovascular safety  
4 information from studies 18 and 19 in Dr. Andraca-  
5 Carrera's talk. I'll briefly discuss other  
6 efficacy data from these trials.

7 There were 16 phase 3 trials that evaluated  
8 the efficacy of dapagliflozin at doses ranging from  
9 1 to 10 milligrams. Results from 11 of these  
10 trials were previously discussed at the 2011 EMDAC  
11 meeting. For presentation purposes, the studies  
12 are grouped as monotherapy, combination therapy,  
13 and special populations.

14 I'll present the summary of the primary  
15 analysis of the individual studies. And integrated  
16 analysis of placebo-controlled trials was also  
17 conducted by Dr. Wei Liu, the statistical reviewer  
18 for this application. Summary data for the changes  
19 from baseline to week 24 in blood pressure, body  
20 weight, glycemic control, and lipid parameters will  
21 be presented.

22 There were two monotherapy trials versus

1 placebo in dapagliflozin, doses of 1 to  
2 10 milligrams conducted in treatment-naïve type 2  
3 diabetes patients. Both measured the primary  
4 endpoint at 24 weeks. One had a 78-week extension  
5 phase.

6           There were nine combination therapy trials.  
7 Four trials added dapagliflozin or placebo to  
8 background single oral agent therapy. One trial  
9 added dapagliflozin or placebo to insulin therapy.  
10 One trial was an active comparator trial against  
11 glipizide. One trial was an add-on to sitagliptin  
12 with or without metformin. And two trials were  
13 combination trials with metformin in drug-naïve  
14 diabetic patients. All trials measured the primary  
15 endpoint at week 24. Extension phases ranged from  
16 24 to 156 weeks.

17           There were five phase 3 trials that  
18 evaluated the efficacy of dapagliflozin in special  
19 populations, including patients with moderate renal  
20 impairment, hypertension, and cardiovascular  
21 disease. Treatment durations were 12 weeks for the  
22 dedicated blood pressure studies but 24 weeks



1 otherwise. Three of the trials included long-term  
2 extension phases of 80 weeks in duration.

3 The primary endpoint in all but one trial  
4 was change in hemoglobin A1c from baseline to  
5 week 24. For study 012, change in body weight from  
6 baseline to week 24 was the primary efficacy  
7 endpoint, with hemoglobin A1c changes as a  
8 secondary endpoint. Additionally, systolic blood  
9 pressure was the co-primary endpoint in two trials,  
10 and two trials had the three-component composite  
11 primary endpoints.

12 I will now discuss some of the efficacy  
13 findings reported for these trials.

14 For the two monotherapy trials,  
15 dapagliflozin was superior to placebo for all  
16 dapagliflozin doses evaluated, with placebo-  
17 subtracted changes from baseline to week 24 and  
18 hemoglobin A1c of minus 0.35 to minus 0.84 percent.

19 For the combination therapy trials in which  
20 dapagliflozin or placebo was added to background  
21 therapy, dapagliflozin again was superior to  
22 placebo for all doses tested, with placebo-

1 subtracted changes of minus 0.38 to minus  
2 0.68 percent. The new data for trial 010,  
3 displayed on the bottom row of the table, included  
4 results, which were consistent with the other  
5 combination therapy trials.

6 There were two studies that compared  
7 dapagliflozin plus metformin to metformin alone and  
8 to dapagliflozin alone. Both the 5- and the  
9 10-milligram dapagliflozin plus metformin  
10 combinations were superior to either dapagliflozin  
11 or metformin alone, with comparator-adjusted  
12 reductions in hemoglobin A1c greater than  
13 0.5 percent.

14 The following two studies were discussed at  
15 the first EMDAC meeting.

16 For the placebo-controlled trial 012, the  
17 primary endpoint was change in body weight at  
18 week 24. Patients randomized to dapagliflozin plus  
19 metformin lost an additional 2 kilograms compared  
20 to those in the metformin-only arm. For the  
21 glipizide control trial, dapagliflozin was  
22 noninferior to glipizide, with equal hemoglobin A1c

1 reductions.

2           This graphic displays the hemoglobin A1c  
3 changes from baseline to week 52 for trial 004, the  
4 active control trial versus glipizide. Of note is  
5 that although noninferiority was observed at  
6 week 52, several earlier time points favored the  
7 glipizide plus metformin treatment arm, depicted  
8 in the bottom line, over the combination of  
9 dapagliflozin plus metformin, depicted as the top  
10 line.

11           In the next few slides, use of dapagliflozin  
12 in special populations will be reviewed. First  
13 I'll discuss renal impairment.

14           The applicant evaluated the pharmacokinetics  
15 and pharmacodynamics of dapagliflozin in type 2  
16 diabetes patients with renal impairment in a  
17 multiple-dose study. On this slide, the vertical  
18 axis depicts urinary glucose excretion and the  
19 horizontal axis estimated glomerular filtration  
20 rate.

21           As the severity of renal impairment  
22 increased, there was an increase in systemic

1 exposure. However, as shown in this slide, despite  
2 the increase in exposure, the 24-hour urinary  
3 glucose excretion decreased with a decline in renal  
4 function, as shown in this graphic from right to  
5 left.

6 The efficacy of dapagliflozin was also  
7 evaluated in a dedicated phase 3 clinical trial  
8 that included patients with moderate renal  
9 impairment, defined as an estimated glomerular  
10 filtration rate of 30 to less than 60 mLs per  
11 minute per 1.73 meters squared.

12 In this trial, both the 5- and 10-milligram  
13 doses of dapagliflozin were not superior to placebo  
14 for the primary efficacy endpoint of change from  
15 baseline to week 24 in hemoglobin A1c. The  
16 applicant is proposing that dapagliflozin not be  
17 used in patients with an eGFR less than 60.

18 For the other special population trials in  
19 patients with hypertension and established  
20 cardiovascular disease, as seen in the next-to-the-  
21 last column in this table, dapagliflozin was  
22 superior to placebo for baseline to week 24 changes

1 in hemoglobin A1c, with all placebo-subtracted  
2 changes greater than or equal to 0.4 percent.

3 For the hypertension trials 073 and 077, as  
4 seen in the top two rows in the next-to-the-last  
5 column, the placebo-subtracted changes in seated  
6 systolic blood pressure of minus 3 and minus 4  
7 millimeters of mercury respectively were  
8 statistically significant.

9 For the two trials in patients with  
10 established cardiovascular disease, as seen in the  
11 bottom two rows in the next-to-the-last column, the  
12 proportion of patients achieve a three-item  
13 endpoint of reduction in hemoglobin A1c, weight,  
14 and systolic blood pressure also were statistically  
15 significant.

16 In all these phase 3 trials, the key  
17 efficacy findings reported by the applicant were  
18 consistent with the agency's analyses. All  
19 superiority comparisons of dapagliflozin versus  
20 placebo for the primary endpoint of hemoglobin A1c  
21 change from baseline to week 24 were statistically  
22 significant, except for the trial conducted in

1 patients with an estimated GFR less than 60.

2 Dapagliflozin was also noninferior to glipizide,  
3 although earlier time points favored the glipizide  
4 treatment arm.

5 To evaluate efficacy in a larger study pool,  
6 Dr. Wei Liu performed additional efficacy analyses  
7 based on a pool of 12 phase 3 placebo-controlled  
8 trials. These analyses excluded the dedicated  
9 renal and 12-week blood pressure trials,  
10 uncontrolled study arms, and selected data from the  
11 combination metformin trials.

12 The endpoints of interest were related to  
13 the known effects of SGLT-2 inhibitors, and  
14 included change from baseline to week 24 in  
15 hemoglobin A1c, fasting plasma glucose, low density  
16 lipoprotein cholesterol, systolic blood pressure  
17 and body weight, and the proportion of patients  
18 achieving a hemoglobin A1c less than 7 percent.

19 Since no adjustments for multiplicity were  
20 performed, these efficacy findings should be  
21 considered exploratory and are intended for  
22 descriptive purposes.

1           The efficacy of dapagliflozin compared to  
2       placebo is observed in the integrated analysis for  
3       the primary efficacy endpoint of hemoglobin A1c  
4       changes from baseline. The placebo-subtracted  
5       changes of approximately minus 0.5 percent are  
6       consistent with the findings from the individual  
7       trials.

8           Across these trials, approximately  
9       20 percent of dapagliflozin-treated patients  
10      achieved a hemoglobin A1c of less than 7 percent,  
11      while 14 percent of placebo-treated patients  
12      reached this goal. Fasting plasma glucose declined  
13      more with dapagliflozin than with placebo.

14          This slide depicts the changes in LDL  
15      cholesterol, body weight, and systolic blood  
16      pressure from baseline to week 24. The graph  
17      depicts absolute changes, and the table below it  
18      shows the corresponding placebo-subtracted changes.

19          In the graph, the placebo arm is represented  
20      as grey cylinders and the dapagliflozin 5- and  
21      10-milligram doses as gold and blue cylinders,  
22      respectively. Dapagliflozin is associated with a

1 2 to 3 milligram per deciliter placebo-subtracted  
2 increase from baseline to week 24 in LDL  
3 cholesterol. This corresponds to approximately a  
4 2 to 3 percent increase from baseline.

5 The placebo-subtracted reductions in weight  
6 at week 24 were approximately 1.4 to 1.8 for the 5-  
7 and 10-milligram doses of dapagliflozin,  
8 respectively. Additionally, the placebo-subtracted  
9 reductions in systolic blood pressure after  
10 24 weeks of treatment were 2 to 3 millimeters of  
11 mercury, similar to what was observed in the two  
12 dedicated blood pressure studies at week 12.

13 Compared to placebo, dapagliflozin was  
14 associated with reductions in fasting plasma  
15 glucose and with small reductions in systolic blood  
16 pressure and body weight. LDL cholesterol  
17 concentrations were greater after 24 weeks compared  
18 to baseline in dapagliflozin-treated patients,  
19 while minimal changes were observed in the placebo  
20 treatment arms.

21 The updated data of the phase 3 trials  
22 provide supportive evidence that dapagliflozin is



1        efficacious for the proposed 5- and 10-milligram  
2        once-daily doses. However, the placebo-subtracted  
3        changes in hemoglobin A1c were modest.

4                In the integrated analyses, dapagliflozin  
5        5 and 10 milligrams were associated with reductions  
6        in fasting plasma glucose and with small reductions  
7        in seated systolic blood pressure and body weight.  
8        However, increases in LDL cholesterol at 24 weeks  
9        were observed.

10              This portion of my presentation will discuss  
11        major safety issues identified during the first  
12        review cycle.

13              The original NDA was submitted in December  
14        of 2010. This information was considered by the  
15        advisory committee in July of 2011. After the  
16        EMDAC meeting, the agency needed additional  
17        information to evaluate the balance between bladder  
18        cancer and hepatic safety risk versus efficacy and  
19        potential cardiovascular benefits.

20              In October 2011, the applicant submitted a  
21        major amendment with additional clinical efficacy  
22        and safety data to address the risk/benefit

1       assessment. I will now briefly review the  
2       applicant's safety database and then discuss major  
3       safety issues.

4               The applicant's pooling strategy for  
5       evaluation of safety in their integrated safety  
6       data sets included two major study pools. The all  
7       phase 2b/3 pool, displayed as the two columns on  
8       the right, consisted of 21 clinical trials,  
9       including both short- and long-term extension  
10      phases, and included all comparators. This study  
11      pool was intended to evaluate less common adverse  
12      events.

13             There were also two pools of placebo-  
14      controlled trials. One contained only controlled  
15      data out to 24 weeks, and the other added data from  
16      control portions of the trial, which extended  
17      beyond 24 weeks.

18             Across the three study pools, the majority  
19      of patients were Caucasian males, age less than 65,  
20      with a body mass index greater than 30 and mean  
21      hemoglobin A1c of approximately 8.1. The mean  
22      duration of diabetes was 7 years.

1           As noted during the first review cycle,  
2       black and African American patients represented  
3       less than 4 percent of the patient population for  
4       the entire clinical program. Baseline  
5       characteristics were generally balanced between  
6       treatment groups. Approximately 30 percent of  
7       patients were from North America.

8           This summary table includes adverse events  
9       for the entire all phase 2b study pool, which  
10      included 9,339 patients. Across all study pools,  
11      the proportion of deaths and patients experiencing  
12      at least one SAE were similar between dapagliflozin  
13      and control treatment arms.

14          Besides the expected increase in the number  
15      of events reported following additional treatment  
16      exposure for this NDA resubmission, no obvious  
17      shifts in the pattern of events were observed since  
18      the first review cycle.

19          This table summarizes the causes of death,  
20      which were reported in at least two patients  
21      randomized to dapagliflozin treatment arms. Many  
22      of the deaths reported after the last review were

1 associated with the cardiac disorder system/organ  
2 class, and with the exception of a single case were  
3 in patients receiving the 10-milligram dose. This  
4 is because 26 of the 37 deaths with dapagliflozin  
5 were from the applicant's long-term trials that  
6 were enriched with patients with established  
7 cardiovascular disease, for which only the 10-  
8 milligram treatment arm was evaluated.

9           There was no clear difference in the causes  
10 of death between dapagliflozin and comparators.  
11 Specific serious adverse events were also examined,  
12 besides bladder and breast cancers, which I will  
13 discuss in the next several slides. There was no  
14 imbalance between dapagliflozin and comparator for  
15 specific types of serious adverse events.

16           I will now discuss bladder cancer, which was  
17 one of the safety concerns identified during the  
18 first review cycle.

19           In the first review cycle, there were  
20 9 reported cases of bladder cancer among  
21 dapagliflozin-treated patients and 1 in the control  
22 arms. All cases were male. Among males, the

1 incident rate ratio was greater than 5, with a wide  
2 confidence band.

3 Since use of dapagliflozin is associated  
4 with increased genitourinary adverse events, an  
5 evaluation of potential detection bias accounting  
6 for the imbalance was undertaken. Neither the  
7 review team nor the applicant at that time were  
8 able to discover evidence of increased surveillance  
9 and thus potential detection bias in dapagliflozin  
10 groups compared to the control treatment arm.

11 For this cycle, the agency required the  
12 applicant to submit additional clinical trial data  
13 to increase patient-years of exposure to  
14 dapagliflozin and comparators.

15 The applicant has now submitted a pooled  
16 30-month updated safety analysis from 21  
17 randomized, controlled phase 2b/3 clinical trials.  
18 These trials enrolled approximately 10,000 patients  
19 and included 40 percent more patient-years of  
20 exposure since the 4-month safety update of the  
21 original submission. The overall median treatment  
22 time is approximately one year.

1           One additional bladder cancer case was  
2       reported in a 53-year-old dapagliflozin-treated  
3       woman. Inclusion of this case in the pooled  
4       analysis results, results in a bladder cancer  
5       incident rate of 0.17 for dapagliflozin-treated  
6       patients compared to 0/03 in the comparator arm.  
7       The incident rate ratio of 6.11 is based on males  
8       and females combined, but is similar to the  
9       previous male-specific one.

10           This table summarizes the 10 bladder cancer  
11       cases reported in the dapagliflozin treatment  
12       patients as of this resubmission. Nine of the  
13       10 reported were diagnosed in men. The mean age  
14       for the total population was 63, and these cases  
15       were reported from nine different countries.

16           Half of the cases were diagnosed in less  
17       than 6 months of exposure. Approximately  
18       70 percent were current or past smokers. Four out  
19       of the 10 were diagnosed after approximately 1 year  
20       of exposure. Pioglitazone use was reported in only  
21       one patient. And 6 patients had hematuria at  
22       baseline.

1           In addition to looking at clinical trial  
2 data, we also looked at postmarketing experience in  
3 other countries where dapagliflozin is approved,  
4 including the European Union and other countries.

5           The Division of Pharmacovigilance examined  
6 the FAERS and Vigibase databases and the medical  
7 literature for potential bladder cancer cases of  
8 dapagliflozin-treated patients. They also looked  
9 at canagliflozin, which is an SGLT-2 inhibitor  
10 approved in the U.S. and other countries.

11           The search identified five bladder cancer  
12 cases in patients treated with canagliflozin and  
13 none in patients treated with dapagliflozin. Based  
14 on the diagnosis dates, these cases were reported  
15 after approval of canagliflozin.

16           Four patients had a current or past history  
17 of smoking. It was acknowledged that bladder  
18 cancer is a relatively common cancer in the mature  
19 adult population, and therefore, assessment of  
20 causality based on these spontaneous reports is  
21 limited.

22           A literature search did not identify

1 additional cases. Additionally, a 15-day safety  
2 report from an ongoing trial was submitted to the  
3 dapagliflozin IND. This case involved a 67-year-  
4 old who presented with hematuria and urinary  
5 retention. He was diagnosed with grade 3 papillary  
6 urothelial bladder cancer of 3 centimeters in size,  
7 which was confirmed by cystoscopy. The event  
8 occurred approximately 4 months after exposure to  
9 dapagliflozin. This patient had a previous smoking  
10 history.

11 Our pharmacology/toxicology colleagues  
12 examined whether there was a bladder cancer signal  
13 in animal studies in the original NDA submission.  
14 In the original NDA submission, 2-year rodent  
15 studies showed no evidence of tumor initiation or  
16 promotion. However, the evaluation of tumor  
17 promotion in these 2-year rodent studies is limited  
18 by lack of background neoplastic or pre-neoplastic  
19 bladder lesions.

20 Pursuant to our action for dapagliflozin in  
21 the first review cycle and following discussion  
22 with the applicant, it was hypothesized the bladder



1 tumor promotion could be secondary to changes in  
2 the microenvironment of the bladder in vivo. Thus,  
3 the FDA recommended the applicant evaluate  
4 dapagliflozin in a rodent tumor promotion model  
5 that simulates the clinical experience.

6 In response to the complete response letter,  
7 the applicant conducted studies that addressed  
8 dapagliflozin as a tumor promoter, but these  
9 studies were independent from in situ changes in  
10 the bladder microenvironment, and results from  
11 these studies showed no evidence of tumor  
12 promotion.

13 Importantly, the submitted studies did not  
14 evaluate dapagliflozin under conditions that  
15 simulate the clinical experience, such as changes  
16 in bladder microenvironment and renal function due  
17 to dapagliflozin, and transitional tumors in the  
18 bladder.

19 So in summary, nonclinical studies  
20 demonstrate that dapagliflozin does not act  
21 directly as a carcinogen. Bladder tumor promotion  
22 secondary to changes in the microenvironment of the

1 bladder and renal function under conditions of  
2 dapagliflozin use is incompletely assessed in an in  
3 vivo nonclinical model of tumor promotion.

4 Besides bladder cancer, there did not appear  
5 to be an imbalance in the overall incidence of  
6 malignancies between dapagliflozin and comparator  
7 treatment arms across the entire dapagliflozin  
8 clinical program. The stratified incident rate  
9 ratio versus control is 1.030, and similar to the  
10 rate ratio reported at the time of the first major  
11 amendment.

12 Although there were no statistically  
13 significant differences between dapagliflozin and  
14 control arm for specific tumor types, there were  
15 numerically higher numbers for other tumor types,  
16 including in musculoskeletal soft tissue,  
17 pancreatic, prostate, and breast cancers. Of these  
18 malignancies, breast cancer was a concern at the  
19 time of the first EMDAC meeting.

20 The Division of Oncology Products was  
21 consulted to review breast cancer cases in the  
22 dapagliflozin clinical program. It was noted that

1 while an increased incidence of breast cancer was  
2 observed in dapagliflozin relative to the  
3 comparator arm, the incident rate ratio in females  
4 was similar to that reported at the time of the  
5 major amendment and lower than the incident rate  
6 ratio at the time of the first EMDAC meeting.

7 It was acknowledged that breast cancers had  
8 other risk factors and potential confounders, and  
9 that the data with regard to breast cancer risk  
10 association with dapagliflozin was inconclusive and  
11 insufficient. In particular, it was noted that the  
12 majority of patients were diagnosed within one year  
13 of exposure.

14 Besides potential cancer risk, hepatic  
15 safety was also a concern during the first review  
16 cycle. Hepatic safety of dapagliflozin was  
17 initially questioned following a single case of  
18 biochemical Hy's law, defined as a serum ALT  
19 greater than or equal to three times the upper  
20 normal reference limit, with a serum total  
21 bilirubin greater than two times the upper  
22 laboratory reference range.

1           The case involved a 78-year-old male exposed  
2           to 2.5 milligrams of dapagliflozin. The patient  
3           had been diagnosed with compound heterozygous  
4           hemochromatosis, and his baseline ALT values were  
5           mildly elevated.

6           Transaminases began to increase  
7           approximately 3 months after initiating drug, and  
8           peaked with an ALT of over 1800 international units  
9           per liter on day 200. And this was associated with  
10          a total bilirubin of 4.2 milligrams per deciliter.

11          Dapagliflozin was discontinued on day 192.  
12          The patient subsequently developed abdominal pain,  
13          nausea, jaundice, and ultimately had a liver biopsy  
14          on day 204. The biopsy report had features  
15          suggestive of autoimmune hepatitis, but other  
16          laboratory tests to support the diagnosis were  
17          negative. Serology did not reveal a viral  
18          etiology.

19          The patient was treated with high-dose  
20          corticosteroids starting on day 349, at which point  
21          hepatic enzymes had already begun to decline. The  
22          opinion of three expert hepatologists to the

1       applicant were mixed concerning the cause of the  
2       patient's abnormal liver test.

3               Following a thorough review by the agency  
4       hepatologists for alternative etiologies, this  
5       event was classified as probable drug-induced liver  
6       injury associated with dapagliflozin.

7               Do we have an audiovisual person?

8               DR. SMITH:   Could we have some technical  
9       assistance?   The slide won't advance.

10              (Brief pause.)

11              DR. PUCINO:   Thank you very much.

12              In the complete response letter, the  
13       applicant was informed that they should submit  
14       additional clinical trial data that includes an  
15       updated review of hepatic safety.   These data  
16       should include cases that meet the definition of  
17       biochemical Hy's Law, and the incidence of marked  
18       laboratory abnormalities should be reported.   The  
19       NDA resubmission included these data.

20              In the dapagliflozin development program,  
21       the applicant treated hepatic adverse events as  
22       events of interest, and standard-measure queries

1        were used to search for hepatic adverse events.

2                The applicant also utilized an independent,  
3        blinded hepatic adjudication committee for  
4        assessment of cases that met the four prespecified  
5        criteria listed in this slide. These criteria were  
6        based on transaminase and bilirubin elevations and  
7        on hepatic adverse events.

8                The two far right columns of this table  
9        display the incidence of hepatic adverse events,  
10       SAEs, and events leading to discontinuation for the  
11       overall dapagliflozin group and the overall  
12       comparator group. The incidences were similar  
13       between dapagliflozin and comparator.

14               The middle column specifically includes the  
15       dapagliflozin 10-milligram group. For this group  
16       there were slightly numerically, but not  
17       statistically significantly, more hepatic SAEs and  
18       discontinuations due to hepatic AEs compared to the  
19       lower doses, but the overall numbers of events were  
20       small.

21               Marked laboratory abnormalities were  
22       reported in the all phase 2b trial and are

1 presented in this table. There were no clear  
2 imbalances in transaminase elevations between  
3 randomized treatment groups, or of most interest,  
4 in patients who exhibited both hepatocellular  
5 injury with liver dysfunction, defined as an AST or  
6 ALT greater than three times the upper limit of the  
7 reference range and a total bilirubin greater than  
8 twice the upper laboratory reference range. And  
9 this is depicted in the bottom row.

10 In the development program, including all  
11 the new data, 81 cases from 80 patients met one or  
12 more of the criteria for inclusion in the liver  
13 adjudication process across the 27 completed  
14 studies. Of these 81 cases, 17 events were  
15 adjudicated as possibly related to study  
16 medication.

17 Ten of the 17 occurred in dapagliflozin-  
18 treated patients compared to 6 in the placebo  
19 treatment arm and 1 patient receiving dapagliflozin  
20 from an open label, single treatment arm study.

21 There were 14 events associated with ALT or  
22 AST greater than three times the upper limit of

1 normal reference range values and total bilirubin  
2 greater than twice the upper limit. Of these  
3 14 cases, 10 occurred in dapagliflozin-treated  
4 patients.

5 The hepatic adjudication committee initially  
6 classified 2 events, both in dapagliflozin-exposed  
7 patients, as possibly related and the other  
8 12 assessed as unlikely or excluded. In this cycle  
9 of three new cases identified in dapagliflozin-  
10 treated patients, all were adjudicated as unlikely.

11 This slide provides a summary of the updated  
12 information on the case I presented a few minutes  
13 ago, which had been adjudicated as probable drug-  
14 induced liver injury associated with dapagliflozin  
15 on the first cycle.

16 Since the first review, this now-84-year-old  
17 patient has had several additional years of  
18 follow-up. As stated earlier, he had been treated  
19 with corticosteroids after his transaminases had  
20 already begun to decline. Transaminases returned  
21 to near-normal levels.

22 Subsequently, transaminases were elevated on



1 two occasions while on azathioprine for presumed  
2 autoimmune hepatitis, and he was off dapagliflozin  
3 at that time. Based on the subsequent review of  
4 two expert hepatologists, the applicant proposes to  
5 reclassify this event as autoimmune hepatitis.

6 The time course of liver abnormalities for  
7 this patient is presented in this slide. Days of  
8 study are depicted on the X axis, and log-fold  
9 increases in liver tests are presented on the  
10 Y axis. Dapagliflozin exposure is indicated in the  
11 white rectangle at the bottom and ended on day 192.  
12 The vertical dotted line in the middle demarcates  
13 the extended follow-up for this review cycle. As  
14 noted to the right of the dotted line, the patient  
15 had at least two transaminase flares while  
16 receiving azathioprine and remaining off of  
17 dapagliflozin.

18 Based on the additional long-term follow-up,  
19 subsequent flares off of study medication, and the  
20 clinical response to immunosuppressives,  
21 Dr. John Senior, the FDA hepatology consultant,  
22 concluded that this case has characteristics of

1 autoimmune hepatitis, but the contribution of  
2 dapagliflozin cannot be excluded.

3 Drs. Senior and Seif [ph] had also evaluated  
4 all of the other cases that met the criteria for  
5 ALT greater than three times the upper laboratory  
6 limit and total bilirubin greater than two times  
7 the upper laboratory limit. And in all these  
8 cases, they felt that there was another etiology,  
9 which was more likely than dapagliflozin exposure.

10 The Division of Pharmacovigilance I was  
11 also asked to review postmarketing reports and the  
12 literature for cases of serious liver injury  
13 associated with dapagliflozin or canagliflozin.

14 Only one report was identified of a patient  
15 randomized to dapagliflozin in an elderly male with  
16 multiple other potential etiologies. This case had  
17 previously been reviewed and excluded by the  
18 hepatic adjudication committee. No additional  
19 information related to hepatic adverse events were  
20 identified in the medical literature.

21 In summary, the majority of cases with  
22 marked elevations in both transaminases and total

1 bilirubin had other diagnoses that were more likely  
2 than dapagliflozin to have caused the test  
3 abnormalities. ALT elevations were generally  
4 balanced across treatment arms.

5 The long-term follow-up of the possible  
6 drug-induced liver injury case is supportive of  
7 autoimmune hepatitis. However, the association  
8 with dapagliflozin cannot be entirely excluded for  
9 this case. One postmarketing case report from  
10 another country had multiple other possible  
11 contributing etiologies.

12 I will now review other adverse events of  
13 interest, starting with common adverse events.

14 The adverse reactions reported in at least  
15 2 percent of patients treated with dapagliflozin  
16 and occurring more commonly than with patients  
17 treated in the placebo arm for the short-term study  
18 pool are included in this slide, and they include  
19 hypoglycemia, genital infections, urinary tract  
20 infections, back pain, and polyuria. As  
21 anticipated with the SGLT-2 inhibitor pharmacologic  
22 class, dapagliflozin was associated with adverse

1 events of genital and urinary tract infections.

2 This slide presents data from the placebo-  
3 controlled short-term study pool, with  
4 dapagliflozin treatment arms represented by the  
5 blue cylinders and placebo controls as the gold  
6 cylinders. Dapagliflozin was associated with  
7 increased risk for genital infections occurring in  
8 5.5 percent of dapagliflozin-treated patients,  
9 compared to 0.6 percent in the control arm.

10 Although no events were serious or severe,  
11 5 dapagliflozin-treated patients discontinued study  
12 due to these events. These events were more common  
13 in females than in males in both treatment arms,  
14 and were more common in dapagliflozin-treated  
15 patients for each gender.

16 Focusing in on the table on the bottom of  
17 the slide, approximately 5 percent of  
18 dapagliflozin-treated patients received  
19 antimicrobial therapy for genital infections, and  
20 infections typically resolved with a single course.

21 Of those dapagliflozin-treated patients who  
22 had genital infections, 17 percent had a recurrent

1 event of genital infections. However, more than  
2 2 events was uncommon. Vulvovaginal mycotic  
3 infections and balanitis were the most common  
4 genital infections reported for women and men,  
5 respectively.

6 Similar to genital infections, dapagliflozin  
7 treatment arms were also associated with an  
8 increased risk for urinary tract infections  
9 compared to placebo, occurring in 4.7 and  
10 3.5 percent of patients, respectively.

11 Predisposing risk factors such as history of  
12 recurrent UTI, benign prostatic hypertrophy, renal/  
13 urinary tract stones, and nocturia were present in  
14 approximately 20 percent of patients in both  
15 treatment arms.

16 UTI events were again more common in females  
17 than in males and typically resolved with  
18 antimicrobial therapy. SAEs and withdrawals due to  
19 UTIs and pyelonephritis were uncommon. Recurrent  
20 events occurred more often in the dapagliflozin  
21 treatment arms.

22 I will now address events of renal

1       impairment and volume depletion and polyuria.

2               The applicant used a customized MedDRA query  
3       to look for events of renal impairment and renal  
4       failure. This graph addresses these events. The  
5       second set of columns includes only patients over  
6       65 years of age. The next set of columns includes  
7       only patients with an estimated GFR between 30 and  
8       60. The far right set of columns includes patients  
9       over the age of 60 with an eGFR of 30 to 60. For  
10      all groups, the incidence or renal impairment  
11      events was numerically higher among dapagliflozin-  
12      treated patients.

13              The overall percentages of patients  
14      experiencing an event and the relative proportions  
15      were increased with this NDA resubmission, which  
16      the applicant attributed to inclusion of patients  
17      with moderate renal insufficiency.

18              In the subgroup analyses, patients who were  
19      over age 65 or had moderate renal impairment at  
20      baseline appeared to be more at risk for renal  
21      impairment events, with the highest proportion of  
22      events reported for individuals with both baseline

1 characteristics.

2 Events of volume depletion were also more  
3 common in patients managed with dapagliflozin  
4 versus a placebo control arm, and this slide  
5 depicts that for patients for total events on the  
6 far left, for patients over 65 in the next set of  
7 columns, for those with an eGFR of 30 to less than  
8 60, and for those receiving loop diuretics. The  
9 events were relatively small in numbers, however.

10 Since hemoconcentration may be associated  
11 with medications that increase urinary output, the  
12 applicant assessed changes in hematocrit. This  
13 slide depicts the changes in hematocrit from  
14 baseline to end of study for both placebo-  
15 controlled study pools, the short-term study  
16 reflected for the cylinders on the left, while the  
17 long-term study pool was represented by the  
18 cylinders on the right.

19 Over 24 and 102 weeks, there was  
20 approximately a 2- to 3 percent increase in  
21 hematocrit in the dapagliflozin groups, while  
22 limited changes occurred in the placebo treatment

1 arms.

2 The applicant also performed a customized  
3 MedDRA query for polyuria events using a  
4 prespecified list of preferred terms that included  
5 pollakiuria -- polyuria, and urine output  
6 increased. As anticipated, dapagliflozin treatment  
7 was associated with an increase in the number of  
8 total polyuria events as well as each individual  
9 component of the MedDRA query.

10 I will next briefly review bone safety,  
11 which was a potential concern with the SGLT-2  
12 inhibitor pharmacologic class. During the first  
13 review cycle, the Division of Reproduction and  
14 Urologic Products was consulted to review bone  
15 safety of dapagliflozin. At that time it was felt  
16 that there was no indication that dapagliflozin  
17 exerts a clinically significant effect on either  
18 bone loss or increased fracture risk.

19 Because dapagliflozin may alter renal  
20 tubular transport of several minerals, cause weight  
21 changes, and effect metabolism of vitamin D, the  
22 applicant considers fractures as an adverse event



1 of interest, and prospectively monitored for  
2 changes in biochemical bone markers and the  
3 occurrence of fractures in the clinical program.

4 In their placebo-controlled short-term plus  
5 long-term study pool, the proportion of patients  
6 with fractures were relatively low and balanced  
7 between dapagliflozin and placebo treatment arms.

8 Based on the data from the placebo-  
9 controlled short-term study pool, the difference  
10 between dapagliflozin and placebo for calcium,  
11 phosphorus, parathyroid hormone, and vitamin D were  
12 small and of uncertain clinical relevance.

13 There were two studies in the clinical  
14 program related to bone safety that I will briefly  
15 discuss. Trial 012 was a 24-week placebo-  
16 controlled trial with a 78-week extension phase  
17 designed to evaluate the effects of dapagliflozin  
18 on bone marrow density.

19 In this trial, the applicant reported no  
20 clinically significant, meaningful changes in bone  
21 biomarkers or bone mineral density, following up to  
22 102 weeks of exposure to dapagliflozin. However,

1       although not statistically significant, a  
2       minus 0.94 percent placebo-subtracted reduction was  
3       observed at the femoral neck, which was associated  
4       with a minus 0.85 percent mean change from  
5       baseline.

6               Trial 029, which was previously discussed,  
7       was intended to evaluate the effects of  
8       dapagliflozin in patients with moderate renal  
9       impairment. In this trial, an imbalance of  
10      fracture events that favored placebo treatment was  
11      observed at week 104. There were 13 events among  
12      dapagliflozin-treated patients and none among the  
13      placebo-treated patients.

14             In a recent communication, the applicant  
15      reported that all fracture events were related to  
16      falls. Seven of the patients had a history of  
17      orthostatic hypotension and diabetic neuropathy.

18             In summary, dapagliflozin is a new molecular  
19      entity in the antidiabetic class known as the  
20      sodium glucose co-transporter-2 inhibitors. The  
21      magnitude of hemoglobin A1c reductions observed in  
22      the dapagliflozin clinical program are relatively

1 consistent across trials and similar to that of  
2 other trials of recently approved antidiabetic  
3 drugs. However, the efficacy is limited to  
4 patients with normal renal function or mild renal  
5 impairment.

6 In addition to improvement in glycemic  
7 control, dapagliflozin produces modest reductions  
8 in body weight and systolic blood pressure.

9 Regarding safety, there continues to be a  
10 numeric imbalance in cases of bladder cancer not  
11 favoring dapagliflozin. An imbalance in bladder  
12 cancer events was not seen with canagliflozin.

13 Additionally, the applicant has provided  
14 additional follow-up data regarding the potential  
15 case of drug-induced liver injury that support a  
16 possible reclassification of this diagnosis as  
17 autoimmune hepatitis. However, an association with  
18 dapagliflozin remains plausible.

19 Across the safety database, the occurrence  
20 of marked liver test abnormalities remain  
21 relatively balanced between both dapagliflozin and  
22 comparator treatment arms.

1           As anticipated with SGLT-2 inhibitors,  
2       dapagliflozin is associated with increases in LDL  
3       cholesterol, adverse events of genital and urinary  
4       tract infections, and in increased events related  
5       to volume depletion and renal impairment. The  
6       potential risk for fractures with long-term use in  
7       vulnerable patient populations is unknown.

8           This presentation represents the valued  
9       contributions of many members of the  
10      multidisciplinary review team. The efforts of  
11      several of these individuals are acknowledged on  
12      this slide. Thank you.

### 13                           **Clarifying Questions**

14           DR. SMITH: Thank you.

15           So what we would like to do in this next  
16      session of the discussion here is to focus  
17      initially particularly on questions for  
18      clarification directed to the FDA. I know there  
19      are other questions that people have, and we will  
20      get to those later on.

21           Dr. Hiatt, I'm aware that you had a data-  
22      related question for the sponsor, and we'll come to

1       that just before we break for lunch so you can get  
2       that request in.

3               DR. HIATT:   Thank you.

4               DR. SMITH:   We'll start with Dr. Lewis.

5               DR. LEWIS:   I asked this question by email,  
6       and I hope that means the analysis might have got  
7       done.

8               One of the hypotheses in the briefing  
9       document is that microenvironment of chronic  
10      inflammation or infection could be the stimulant  
11      for bladder cancer.  And although those are usually  
12      not transitional -- they're squamous cell -- I  
13      thought that was an interesting hypothesis.

14              That microenvironment of glucosuria and  
15      infection would be present with cana, whatever,  
16      gliflozin, and you have access to that database.  
17      So I thought it would be helpful to know what the  
18      bladder cancer experience was numerically -- I sat  
19      on the board so I know there wasn't a horrible  
20      imbalance; but it would make a difference if it was  
21      zero cana and 10 active control, or if it was 6 and  
22      3.

1           Do you have that information? Because  
2           that's an important source to help better inform  
3           us.

4           DR. PUCINO: Yes. There was no safety  
5           signal during the canagliflozin development  
6           program, obviously.

7           DR. LEWIS: Right.

8           DR. PUCINO: From when I've looked at the  
9           reviews, I had not noticed that there was cases of  
10          bladder cancer. But we'll go back and we'll have  
11          to confirm that.

12          DR. LEWIS: Thank you.

13          DR. SMITH: Dr. Wyndham Wilson.

14          DR. W. WILSON: So I wanted to get at this  
15          possible class effect of the SGLT-2 inhibitors in  
16          early cardiovascular events.

17          You provided data showing that with the one  
18          that's been approved -- I'll call it cana -- that  
19          there was an increased rate. And you're also  
20          hypothesizing that possibly that's the case with  
21          dapa as well. So my question is, number one, was  
22          the patient characteristics of the cana trial

1 similar to that of the dapag trial?

2 Number two, the sponsor did a hazard ratio  
3 analysis over time where they showed that the first  
4 30-day hazard ratio of cardiovascular events was  
5 unchanged over time. And so my other question is,  
6 did you do a similar hazard ratio analysis over  
7 time for cana as well?

8 DR. ANDRACA-CARRERA: I can try to answer  
9 those questions.

10 So the first is the characteristics of the  
11 patients on canagliflozin. The imbalance was  
12 observed in canagliflozin on the dedicated  
13 cardiovascular outcomes trial, which was a trial  
14 with an enriched population with high baseline  
15 cardiovascular risk. In the rest of the  
16 canagliflozin program, the other phase 2 and phase  
17 3 trials, there was no such imbalance observed. So  
18 it's only in the dedicated cardiovascular outcomes  
19 trial.

20 The sponsors for canagliflozin also showed a  
21 similar plot of how the hazard ratio is variable  
22 through time through the development program, and

1       it looks similar to dapagliflozin. It is possible  
2       that this is a chance finding, but since in both  
3       dapa and cana we observed it within the first 30  
4       days, we thought it would be relevant to raise it  
5       here.

6               DR. W. WILSON: I think that's worthwhile.  
7       But if in fact the hazard ratios don't change over  
8       time, that speaks a little bit to this possibly  
9       being a chance finding.

10              Were there more people with renal  
11       dysfunction in the cana trial? Because it appears  
12       as though patients who have lower renal functions  
13       are the ones that seem to have more problems with  
14       volume loss; at least that's what I thought I say.

15              DR. GUETTIER: For the canagliflozin  
16       program, the CANVAS trial was enriched with people  
17       with renal dysfunction. Also, to get back to  
18       your first point, we looked at the baseline  
19       characteristics of patients enrolled in CANVAS who  
20       had events and compared that to the baseline  
21       characteristics of the overall population, and we  
22       were unable to find a difference between patients



1       that had events and any overall population.

2               DR. SMITH: I wanted to extend that question  
3       for a few more details, specifically regarding the  
4       early events in the dapa studies, the early  
5       cardiovascular events.

6               We heard the question about renal function.  
7       And in terms of hypothesis-generating probing, I'm  
8       wondering in terms of blood pressure, in terms of  
9       the nature and timing of possible cardiovascular  
10      events that may have defined them as having  
11      existing cardiovascular disease. And I'm wondering  
12      about other medications, including, for example,  
13      anticoagulants.

14              So the question is, how much did you probe  
15      those in detail?

16              DR. PUCINO: Probably the applicant might be  
17      able to best address this. But when we looked at  
18      the actual case reports, it wasn't so clear. These  
19      are all people with truly established disease.  
20      Several had recurrent events, i.e., stroke and  
21      heart attack.

22              DR. LIST: I'd be happy to address it, if

1       you'd like.

2               DR. LIST: I'd be happy to address this if  
3       you like.

4               DR. SMITH: Yes. That would be helpful.  
5       And again, I know this is a hypothesis-generating  
6       question. But I'm wondering how far you went with  
7       that and what you looked at.

8               DR. LIST: Yes. With the small number of  
9       events, but looking at what cana also had, we did  
10      look into this hypothesis that volume depletion  
11      could have something to do with early events with  
12      dapagliflozin. There are eight early primary  
13      endpoint events: 3 strokes, 2 myocardial  
14      infarctions, 1 cardiovascular death, and  
15      2 hospitalizations for unstable angina.

16              We've looked at that for evidence of volume  
17      depletion, first looking at, did those patients  
18      have events of volume depletion? And the answer  
19      was no. We looked at it for evidence of volume  
20      depletion by their change in hematocrit, and their  
21      change in hematocrit was not different from the  
22      change in hematocrit -- it was actually a little

1       less than the rest of the program.

2               We looked at their baseline blood pressure  
3       and change in blood pressure, and again, the  
4       changes here were not different from the rest of  
5       the program. And then we looked within the  
6       individual cases to see, is there some other data  
7       within the case histories that would help explain  
8       these?

9               What we did see was curious in that 4 of  
10       the cases actually seemed to have evolving  
11       cardiovascular events at the time of randomization.  
12       The 2 unstable anginas were patients who had  
13       actually had symptoms and were referred to a  
14       cardiologist, but didn't see the cardiologist till  
15       after randomization.

16               Two of the 3 strokes had symptoms of their  
17       stroke before randomization, one of whom was  
18       actually being treated for a hypertensive crisis.  
19       So it wasn't really a low blood pressure situation,  
20       but actually had a systolic blood pressure of over  
21       200 at the time of the stroke.

22               So our assessment is, given the small number

1 of cases, we still can't completely rule out that  
2 there's some sort of an early event. But the data  
3 we get from the cases, along with the fact that the  
4 initial hazard ratio is not different from later  
5 time points, leads us to assess that there's no  
6 solid evidence for it.

7 DR. SMITH: Thanks. That's very helpful.

8 Okay. Dr. Packer?

9 DR. PACKER: I just wanted to ask about the  
10 same issue I asked the sponsor. When you did your  
11 meta-analysis of cardiovascular events, did you  
12 consider the issue of censoring?

13 DR. ANDRACA-CARRERA: What we looked at is  
14 the follow-up in the different trials comparing the  
15 two treatment arms. And in all the trials, the  
16 follow-up was comparable in both treatment arms.

17 DR. PACKER: But that's not reassuring, as  
18 you know. Do you know how many patients did not  
19 have follow-up for the planned duration of double-  
20 blind therapy?

21 DR. ANDRACA-CARRERA: I don't have that with  
22 me. Perhaps the sponsors have the information.

1 DR. PACKER: We'll hold that question until  
2 we get that.

3 So when a patient was lost, came off study  
4 drug, you censored the patient for follow-up for  
5 events?

6 DR. ANDRACA-CARRERA: No. It actually  
7 depends -- well, there's two sponsors, and they  
8 have different follow-up rules for how the events  
9 are included. Perhaps they can talk more about it.

10 But one of them, it's 30 days after  
11 discontinuation, I believe, and the other one is  
12 full follow-up until the patient basically  
13 discontinues from follow-up. So patients were  
14 followed after they discontinued treatment.

15 DR. PACKER: Well, 30 days would be terribly  
16 insufficient. A full follow-up is the best  
17 approach, but it depends on how well it was done.  
18 So these issues are very major issues in  
19 interpretation of a meta-analysis. And let me just  
20 make sure that I understand.

21 You created your meta-analysis by -- it was  
22 a stratified approach. You did a Cox proportional

1 hazard ratio. You didn't do a pooled odds ratio.  
2 Right?

3 DR. ANDRACA-CARRERA: It's stratified. It's  
4 stratified by trial.

5 DR. PACKER: Stratified by trial.

6 DR. ANDRACA-CARRERA: Yes.

7 DR. PACKER: By definition, the trials that  
8 have the greatest number of events and the longest  
9 duration of follow-up carry the greatest weight?

10 DR. ANDRACA-CARRERA: Well, it's a hazard  
11 ratio. So the hazard ratio, we didn't find any  
12 evidence of heterogeneous hazard ratio across  
13 trials. Trials with an enriched population had a  
14 higher rate just because there are people that have  
15 higher risk. We didn't find a heterogeneous hazard  
16 ratio across trials, if that's what you're asking.

17 DR. PACKER: That's not what I'm asking.  
18 But I'll hold that question for the sponsor.

19 DR. SMITH: Dr. Peter Wilson.

20 DR. P. WILSON: So from the FDA perspective,  
21 it looks like you changed tack a little bit to get  
22 more events with adding the post-CVD patients. Is

1       that right, from two years ago?

2               DR. GUETTIER: I think what I stated in the  
3       introductory remarks was that we know that there  
4       was additional cardiovascular data available after  
5       the 2011 AC. And since we were dealing with  
6       serious identified risks at the time, we thought  
7       that we would get more information just to see  
8       where the trend was going.

9               So we asked for an additional meta-analysis.  
10      It just so happened that two of the additional  
11      trials were trials that were done in an enriched  
12      patient population, and we looked at those  
13      specifically because we thought they would best  
14      inform cardiovascular risk.

15              DR. P. WILSON: I agree with what you did.  
16      The question I guess I have is related to, there  
17      just are fairly low event rates, and you're looking  
18      for events. It reminds me of trials that had the  
19      number of events prespecified, and you needed more  
20      events to really get robust and solid estimates of  
21      the comparison groups.

22              Leading back to that, although you've

1 retained them, how helpful are the individuals who  
2 have never had an event, and so they're having  
3 their first event? Because some of those, they're  
4 fairly young and they're just not going to have any  
5 events, or it's very unlikely.

6 I know they're diabetic patients, but the  
7 40-year-old on an oral hypoglycemic is really  
8 unlikely to have a cardiovascular event. So have  
9 these estimates and you have person-year estimates,  
10 but they're just not very helpful at all.

11 What I'm getting at is, I think, similar to  
12 what Milt Packer was going after, is more events  
13 and more safety confidence, especially in those who  
14 are likely to have events.

15 DR. PACKER: Yes. Part of the problem, just  
16 to iterate this, if you're going to increase your  
17 confidence, the best way, of course, to collect  
18 events is to take the patients you have and follow  
19 them for the planned duration of therapy. That's  
20 the best and it's the least biased.

21 It's not all that useful to simply add other  
22 components to a combined endpoint because sometimes



1     you're adding components, which are comparing  
2     apples and oranges. For example, although the  
3     sponsor didn't emphasize this, the sponsor had a  
4     secondary endpoint, which included hospitalization  
5     for heart failure, which is a very different  
6     cardiovascular issue than MI and stroke and  
7     cardiovascular death, particularly if you're  
8     dealing with a drug that has a diuretic property.

9             So in this particular -- when you broke down  
10    the components, there was a favorable effect on  
11    hospitalizations for heart failure, which is not an  
12    assessment of cardiovascular safety because it's  
13    from the diuretic effect of the drug. If you put  
14    it in, you dilute out your estimates. You shift  
15    them to the null or more favorable direction.

16            So it's better to stick with the primary  
17    endpoint. But honestly, the preferred endpoint is  
18    your MACE endpoint, which you've insisted on. That  
19    is tried and true. The problem with that is that  
20    if you focus on MACE, the number of events goes  
21    down.

22            DR. ROSEBRAUGH: Yes. Let me just back us

1 up and give a little more of an overview so you  
2 understand when we do -- in a development program,  
3 what the idea behind the guidance was is that there  
4 was going to be some sort of cardiovascular  
5 evaluation. But you always have this tension on  
6 how dedicated a trial should be versus not blocking  
7 development.

8           So we came up with this two-stage approach,  
9 where people could do their typical development and  
10 they use their typical patients, which are probably  
11 not the ones we would really want in a dedicated  
12 study. But that doesn't block them from doing  
13 their development, and it gives us some idea of  
14 what's going on, and we can see if there's  
15 something we should be nervous about.

16           Then they do a dedicated study. So it goes  
17 to your point of, you want higher risk patients.  
18 We all realize that. It's just that we are trying  
19 to find a happy medium between allowing the  
20 development to go forward and not blocking it,  
21 getting some idea if it's okay for marketing, and  
22 then they can do a dedicated study, which is what

1       they're doing. So that's the first issue.

2               The second issue goes to yours. For a  
3       safety study, a noninferiority safety study, we  
4       insist on MACE, for all the reasons you just said.

5               DR. PACKER: I strongly endorse that. There  
6       are all sorts of really good reasons to do that.  
7       And in fact, to a certain degree, I would say that  
8       that should be -- I don't care if it's specified as  
9       the primary analysis. That should be the primary  
10      focus.

11              DR. ROSEBRAUGH: That's why we present MACE  
12      to you folks, so you can see what the MACE is  
13      without the noise.

14              DR. PACKER: Exactly. But the tension  
15      between not slowing development and still getting a  
16      good estimate, it's a wonderful tension. But it's  
17      really tricky, and it's particularly tricky when  
18      patients are being censored during follow-up.

19              DR. ROSEBRAUGH: Right.

20              DR. P. WILSON: So we'll talk about that  
21      later because I must have read your guidance four  
22      or five times. It's actually one of the most

1       fascinating documents, and there are things in it  
2       that you may not have intended to write. But they  
3       have some great wisdom in it.

4               (Laughter.)

5               DR. ROSEBRAUGH: Well, the ones that were  
6       unintended with wisdom I wrote.

7               DR. PACKER: What's that?

8               DR. ROSEBRAUGH: The ones that were  
9       unintended with wisdom I wrote. But that others  
10      are somebody else.

11              DR. PACKER: No, no. I thought you wrote  
12      the wise parts of it.

13              DR. SMITH: Is that follow-up, Dr. Wilson?

14              DR. P. WILSON: Just a quick follow-up. I  
15      think partly also to mesh, I think, with what  
16      Dr. Packer was saying, it would be helpful to have  
17      some of these meta-analyses in the future also be  
18      reported on a person basis, not just a person-years  
19      basis, for exposures and metabolic type diseases  
20      because we especially are interested, of course, at  
21      different intervals.

22              There's a signal of some concern, a very

1 short interval. But the big interval is how many  
2 people for one year-plus, two years-plus, in terms  
3 of safety. So as moving forward, not to do just  
4 meta-analyses on person-years.

5 DR. SMITH: Dr. Lewis, is it on the same  
6 point?

7 DR. LEWIS: No.

8 DR. SMITH: Okay. Then Dr. Thomas, please.  
9 We'll get right back to you.

10 DR. THOMAS: Just hopefully a quick  
11 question. There's another agent in the same class  
12 available in the U.S., and dapa's available in  
13 other countries. And you've presented data that  
14 there aren't really anything alarming in terms of  
15 the databases that are available.

16 Just curious in terms of the prescriptions  
17 filled or prescriptions written to see how useful  
18 that information is. For example, if there only  
19 10,000 prescriptions written, it's not very useful,  
20 versus maybe if there's 100,000 or a million  
21 prescriptions.

22 DR. PUCINO: Yes. We didn't do a comparison

1 of prescription volumes, but we can certainly do  
2 that.

3 DR. SMITH: Dr. Lewis?

4 DR. LIST: May I?

5 DR. SMITH: Yes. Please go ahead.

6 DR. LIST: Dapagliflozin, there have been  
7 over 35,000 patients treated worldwide to date.

8 DR. SMITH: Dr. Lewis?

9 DR. LEWIS: Could you please comment on what  
10 if any penalties are in place for failure to  
11 recruit in DECLARE? There are only 1400 people  
12 enrolled in a potential population of 17,000, and  
13 we all know that once the drug is approved,  
14 enrollment, I would imagine, would be challenging.  
15 Are there any plans by the FDA that they have to  
16 finish the study or else?

17 DR. GUETTIER: Yes. The cardiovascular  
18 safety guidance allows the applicant to market the  
19 drug if they meet the 1.8 margin, which they have.  
20 But it also stipulates that they have to meet a  
21 higher level of precision with regards to the  
22 cardiovascular risk. And so that is usually part

1 of a postmarketing required study, so it's  
2 enforceable by law.

3 DR. PACKER: The guidance, when it says 1.8,  
4 doesn't say how many events need to form the basis  
5 of the 1.8. So I just want to talk about that a  
6 little bit more later on because that's a critical  
7 way of -- you intended the guidance to be useful  
8 and to be helpful. But there are ways in which  
9 someone could take the guidance and misconstrue it  
10 in a way that would not be informative to you.

11 DR. SOUKUP: Matt Soukup, team lead, CDER,  
12 within the Office of Biostatistics.

13 Yes. In the guidance, we don't give any  
14 specifics on how to power the studies. I would say  
15 we're almost always seeing studies that are powered  
16 at 90 percent, assuming a hazard ratio of 1. So  
17 there's a null effect.

18 DR. PACKER: That's in a definitive study,  
19 not in a meta-analysis.

20 DR. SOUKUP: That's with meta-analysis, too.  
21 So they're also developing programs around to  
22 observe a certain number of events. They're doing

1       it in various ways, different sponsors. So they're  
2       looking for about 122 events. Some are looking at  
3       very different scenarios, where they can look  
4       earlier as well.

5               DR. PACKER: 122 events? I'm sorry, but how  
6       did anyone come up with that number?

7               DR. SOUKUP: If you do your power  
8       calculations, it's the way the math works out with  
9       the log rank test statistic.

10              DR. PACKER: The reliability of a result is  
11       not really determined by the confidence interval.  
12       It's determined by the number of events. So I can  
13       show you lots of cardiovascular trials where there  
14       are 50, 70 events with extremely favorable point  
15       estimates and confidence intervals, which are not  
16       replicated at all in a definitive study.

17              So I just want to make sure that I  
18       understand how many events you're asking the  
19       sponsor to deliver.

20              DR. ROSEBRAUGH: Yes. You're right. And I  
21       don't know if we want to get into this right now,  
22       but I'll try to keep it very short.



1 DR. SMITH: You have one more minute.

2 DR. ROSEBRAUGH: For the 1.8, we are silent  
3 on the number of events. And there were a  
4 multitude of reasons behind that; I'm not going to  
5 get into all of it.

6 But as Matt said, if you do power  
7 calculations for 1.8 -- which we realize is not  
8 going to be a definitive answer, but it's mainly  
9 just to look and see if we should be concerned and  
10 it gives us some idea of a point estimate -- we  
11 usually like to have around 120 events, realizing  
12 everything you just said.

13 DR. PACKER: Again, I don't want to belabor  
14 this. So I'll just hold. This is a really  
15 important discussion, and we'll hold it for  
16 afterward.

17 DR. SMITH: Yes. Let's come back to it  
18 later on if it's really critical because we'll have  
19 lots of time later.

20 Dr. Hiatt, assuming you're there, you had a  
21 question for the sponsor, I believe, this morning  
22 that I know about that might be asking for some

1       more data. Is that correct?

2               (No response.)

3               DR. SMITH: Well, what we'll do, we'll  
4 follow that up offline, and we'll communicate with  
5 the sponsor offline as well if there's something  
6 there.

7               So we're now going to break for lunch.  
8 We'll reconvene again in this room in  
9 50 minutes -- that is at 1:00 p.m. -- at which time  
10 we'll begin the open public hearing session.

11              Please take any personal belongings you may  
12 want with you at this time. Committee members,  
13 please remember that there should be no discussion  
14 of the meeting during lunch amongst yourselves,  
15 with the press, or with any member of the audience.  
16 Thank you.

17              (Whereupon, at 12:11 p.m., a luncheon recess  
18 was taken.)

19

20

21

22

A F T E R N O O N    S E S S I O N

(1:02 p.m.)

**Open Public Hearing**

DR. SMITH: So we will start the afternoon part of the schedule. Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

Likewise, FDA encourages you at the

1 beginning of your statement to advise the committee  
2 if you do not have any such financial  
3 relationships. If you choose not to address this  
4 issue of financial relationships at the beginning  
5 of your statement, it will not preclude you from  
6 speaking.

7 The FDA and this committee place great  
8 importance in the open public hearing process. The  
9 insights and comments provided can help the agency  
10 and this committee in their consideration of the  
11 issues before them. That said, in many instances  
12 and for many topics, there will be a variety of  
13 opinions. One of our goals today is for this open  
14 public hearing to be conducted in a fair and open  
15 way, where every participant is listened to  
16 carefully and treated with dignity, courtesy and  
17 respect. Therefore, please speak only when  
18 recognized by the chair. Thank you for your  
19 cooperation.

20 Will speaker number 1 please come to the  
21 microphone. State your name and any financial  
22 relationships you wish to report.

1 DR. ALMASHAT: Thank you very much. My name  
2 is Sammy Almashat. I'm a physician with Public  
3 Citizen's Health Research Group, and I'm presenting  
4 testimony on behalf of Dr. Sidney Wolf, the founder  
5 and senior advisor of the health research group.  
6 And we have no financial conflicts of interest.

7 Unfortunately, I don't have the slide mover,  
8 so do I just announce when the next slide comes up?

9 DR. SMITH: Yes. Why don't you start, and  
10 you can ask for that at first, and they may bring  
11 you a controller here.

12 DR. ALMASHAT: Okay. Next slide, please.

13 In July 2011, Public Citizen testified  
14 against the original dapagliflozin submission for  
15 approval. At the time, dapa would have been the  
16 first of a new chemical class of agents for type 2  
17 diabetes mellitus, the first type 2 diabetes drug  
18 to act at the renal sodium-glucose transport  
19 protein subtype 2. At the time, the approval  
20 request would have been based solely on surrogate  
21 efficacy, hemoglobin A1c lowering as with previous  
22 type 2 diabetes drugs. No evidence of any improved

1 clinical outcomes were demonstrated, unlike older  
2 drugs such as metformin. And at the time of the  
3 overall question, according to the FDA, was whether  
4 the surrogate efficacy of dapagliflozin needs to be balanced  
5 against safety signals identified in the clinical  
6 trials. And of course, the drug was turned down by  
7 a vote of 9 to 6.

8 Fast forward two years, and little has  
9 changed in the dapagliflozin regulatory packet for approval.  
10 The approval is still based on surrogate efficacy  
11 of HbA1c. There is no evidence of any improved  
12 clinical outcomes. What has changed is that in the  
13 past year, a drug with an identical mechanism of  
14 action in the same class has now been approved,  
15 canagliflozin. And the question, according to the  
16 FDA, currently is whether the efficacy of dapagliflozin  
17 needs to be balanced against safety signals  
18 identified in the clinical trials; except we would  
19 point out crucially, it also now needs to be  
20 compared with the safety signals with cana.

21 We believe this to be the case for the  
22 following reasons. For one, the surrogate efficacy

1 on hemoglobin A1c is not significantly different  
2 between dapa and cana. The cardiovascular risks,  
3 the genital infections, polyuria, hypovolemia,  
4 hypotension, and increased LDL are also similar for  
5 the two drugs. But several other major risks of  
6 dapa are not present with cana, and these will be  
7 discussed in the following slides.

8 It's interesting to speculate whether had  
9 the original dapa review in 2011 followed rather  
10 than preceded cana, the vote against its approval  
11 would likely have been even more negative than it  
12 was -- at the time, it was 6 for, 9  
13 against -- because of the unfavorable safety  
14 comparison with cana.

15 In 2011, the following safety problems were  
16 identified in the dapa clinical trials: 9 cases of  
17 bladder cancer in dapa versus 1 in controls; 9  
18 cases of breast cancer in dapa patients versus 1 in  
19 controls; 1 probably Hy's law hepatotoxicity case  
20 classified at the time as a probable diagnosis of  
21 mild to moderately severe dapa-induced liver  
22 injury; increased genital and urinary tract

1 infections; and chronic osmotic diuresis with cases  
2 of prerenal azotemia, hypovolemia, and risks of  
3 dehydration and heat intolerance, especially in the  
4 elderly using diuretics.

5           Regarding the bladder cancer risk, in 2011,  
6 the FDA noted in its briefing document that the  
7 baseline characteristics of risk factors for  
8 bladder cancer in the dapagliflozin-treated patients in the  
9 control group were similar, reducing the likelihood  
10 that any such imbalance of risk might have  
11 contributed to the numerically higher number of  
12 cases observed with dapagliflozin.

13           With 9 cases of bladder cancer occurring  
14 during this time, the rate amounts to approximately  
15 300 per 100,000 subject years. This is compared to  
16 approximately 60 new cases per 100,000 subject  
17 years and controls for an incidence rate ratio of  
18 approximately 5.

19           This table shows the difference in risk for  
20 bladder cancer observed in the clinical trials for  
21 dapagliflozin versus canagliflozin. As we mentioned earlier, there  
22 were 9 cases in the dapagliflozin group versus 1 in



1 controls. In the cana trials, there were 5 cases  
2 in cana patients versus 4 in controls. And on the  
3 right side, you see the p values using a  
4 conservative Yates' correction for chi square. And  
5 what you see is a p value of .83 for cana but .15  
6 for dapa.

7 Now although not statistically significant  
8 by the standard used for the evaluation of efficacy  
9 for which these clinical trials are adequately  
10 powered, it is nevertheless useful information,  
11 especially considering the lack of evidence of any  
12 dapa benefit compared to cana. P equals .15 means  
13 that there is only a 15 percent probability that  
14 this increased bladder cancer with dapa could occur  
15 by chance. In contrast for cana, a p of .83 means  
16 an 83 percent probability of this difference can be  
17 explained by chance; in other words, that the drug  
18 isn't associated with bladder cancer.

19 Now, there have been contradictory arguments  
20 put forth to explain away the bladder cancer risk.  
21 The first argument is that if a chemical or drug  
22 only causes cancer in animals, despite an

1 underpowered ability for human detection, it is not  
2 rally a human carcinogen. But at the same time, if  
3 human cancer is found in a randomized controlled  
4 trial with indistinguishable baseline  
5 characteristics in both groups, but animal evidence  
6 is lacking, again, it is not really a human  
7 carcinogen. So either way, to some people you can  
8 never truly prove that something is carcinogenic.

9         The preclinical and animal studies showed  
10 that dapa did not cause in vitro stimulation of  
11 human bladder transitional cell carcinoma or  
12 increase the size of human TCC tumors implanted in  
13 mice, and dapa did not cause transcriptional  
14 changes characteristic of tumor promoters in a ZDF  
15 rat model. In addition, increased glucose  
16 concentrations did not increase the rate of growth  
17 in TCC cell lines.

18         In response, the FDA noted in the current  
19 briefing document that each of these experimental  
20 approaches had deficiencies in terms of limitations  
21 or relevancy. Results of these studies confirm  
22 what the FDA already concluded, that dapa by itself

1       does not act as a carcinogen, but that any putative  
2       human bladder risk from dapa would likely be  
3       related to tumor promotion secondary to changes of  
4       the micro environment to the bladder in vivo.

5               Now, it's not uncommon that human evidence  
6       for carcinogenicity precedes animal evidence, in  
7       some cases by many years. The story of inorganic  
8       arsenic is a case in point. According to the  
9       partially NIH-funded IARC, over the years, it has  
10      been difficult to provide animal evidence for the  
11      carcinogenesis of inorganic arsenic compounds.

12             More recently however, with animal exposure  
13      to inorganic arsenic during early life, the links  
14      have now been found. And in this case, animal  
15      evidence was found experimentally, long after human  
16      evidence of arsenic-induced bladder cancer.

17             In terms of the breast cancer risk, in 2011,  
18      the FDA noted that breast cancer risk factors at  
19      baseline were similar between the dapa-treated  
20      patients and the control patients. With 9 cases of  
21      breast cancer observed in the female dapa-treated  
22      patients versus none in the comparator arms of the

1       dapa trials, it is technically not feasible to  
2       estimate the incidence rate ratio; that the  
3       age-specific incidence rates of breast cancer were  
4       higher than those reported in the literature could  
5       be a safety signal that dapa may be associated with  
6       an increased risk of breast cancer.

7               The SIR calculated by the sponsor using SEER  
8       data as an external reference group may be  
9       underestimated and is not reassuring due to subject  
10      limitations.

11             The FDA now says that the decline in the  
12      incidence risk ratio over time, the lack of  
13      screening mammography prior to study entry, coupled  
14      with the occurrence of the breast cancers within  
15      the first year of dapa therapy, in addition to the  
16      median time frame diagnosis of diabetes of seven  
17      years, the history of prior exposure to other oral  
18      anti-hypoglycemics, and the hormone receptor  
19      positivity of the breast cancers all suggest that  
20      the increased incidence of breast cancer is a  
21      spurious finding.

22             However, we would note that to call this a

1       spurious finding in light of the extremely closed  
2       baseline characteristics and the randomized nature  
3       of the study is itself somewhat questionable.

4               The potential liver toxicity of  
5       dapagliflozin is important to consider in light of  
6       a 2007 draft FDA guidance, which stated that pure  
7       hepatocellular injury sufficient to cause  
8       hyperbilirubinemia is an ominous indicator of the  
9       potential for a drug to cause serious liver injury.

10              In the current FDA briefing document, they  
11       note that finding one Hy's law case in a clinical  
12       trial database is worrisome. Clinical trials of  
13       tasosartan and ARB showed a single Hy's law case.  
14       This led to a request for a much larger  
15       premarketing database, and the drug was ultimately  
16       abandoned.

17              Recent examples of some drug causing  
18       idiosyncratic hepatotoxicity such as bromfenac,  
19       troglitazone, and ximelagatran further illustrate  
20       the predictive value of Hy's law, where findings  
21       during clinical trials -- in some cases, even a  
22       single finding -- were noted, and severe

1 drug-induced liver injury occurred after marketing.  
2 And again, it's important to note the comparison  
3 with cana, which is already on the market and  
4 available to patients.

5           There was an imbalance and marked shifts in  
6 transaminases not favoring cana in the clinical  
7 trials, but a review of cases that met the  
8 biochemical criteria of Hy's law did not identify  
9 any true Hy's law cases with cana. Thus, according  
10 to the FDA in the cana briefing documents, the  
11 absence of a Hy's law case was reassuring.

12           In terms of the genital and urinary  
13 infections, seen with both drugs, by the way, in  
14 dapa's case, in 2011, a significant increase in  
15 vulvovaginal mycotic infections and vaginal  
16 infections were seen with dapa patients at a rate  
17 of around 2.4 percent, which is approximately 5  
18 times higher than the rate seen in placebo  
19 patients.

20           In the current briefing documents, it's  
21 noted that urinary tract infections significantly  
22 increased in all dapa patients compared with the

1 placebo patients.

2 Now, both cana and dapa have significantly  
3 increased genital mycotic infections. The  
4 difference is in degree. This table is a visual  
5 representation of the rates of urinary tract  
6 infections seen in the clinical trials for both  
7 drugs.

8 In dapa's case, 8.2 percent of patients  
9 treated with the drug acquired a UTI versus  
10 6.2 percent of controls, approximately a 33 percent  
11 increase. In cana's case, 5.6 percent treated with  
12 cana developed a UTI compared with 4.6 percent on  
13 placebo, an increase of approximately 20 percent.

14 Now again, you see on the right using the  
15 conservative Ky chi square Yates correction, you  
16 see that the probability that these are chance  
17 findings is much lower with dapa as opposed to cana  
18 given the higher risk seen in the trial. And  
19 finally, the risk of chronic intermittent osmotic  
20 diuresis and volume depletion has to be considered  
21 given that that's inherent to the drug's mechanism  
22 of action.

1           There was an increase in volume depletion  
2       events in people randomized to dapa, such as  
3       hypotension, mainly after three weeks of therapy,  
4       compared with patients getting a placebo, a rate of  
5       approximately .7 percent in dapa versus .4 percent  
6       in placebo.

7           Now again, although this did not reach  
8       statistical significance for a trial not adequately  
9       powered for safety, there is still a high  
10      probability of its relationship to dapa, especially  
11      because of the clear biologic plausibility. And  
12      the decreases in the estimated glomerular  
13      filtration rate and increases in blood urea  
14      nitrogen, relative to serum creatinine, suggest  
15      development of prerenal azotemia; again, nothing  
16      surprising given the mechanism of action of these  
17      drugs.

18           Dapa and cana share certain features in  
19      common. The efficacy of both is based solely on  
20      surrogate markers, hemoglobin A1c lowering as with  
21      previous type 2 diabetes drugs without evidence of  
22      any improved clinical outcomes, contrary to an



1       older drug such as metformin, which does  
2       demonstrate improved clinical benefit. They also  
3       share the cardiovascular risks, general infections,  
4       increased LDL, osmotic diuresis with polyurea,  
5       hypovolemia, hypotension, dehydration, and heat  
6       intolerance, especially in elderly patients.

7               What's critical to consider in today's  
8       approval decision are the differences. In terms of  
9       bladder cancer, again, the chances that the  
10      increased risk was due to chance alone in dapa's  
11      case is 15 percent; for cana, 83 percent. The  
12      single Hy's law case seen in the dapa trial also  
13      stands out as opposed to cana.

14             In the case of dapa, it was concluded that  
15      there was a probable diagnosis of mild to  
16      moderately severe dapa-induced liver injury. And  
17      again, precedence suggests finding one Hy's law  
18      case in a clinical trial database is worrisome. In  
19      addition, there was asymmetry seen with urinary  
20      tract infections with dapa, causing approximately a  
21      33 percent increased risk in such infections during  
22      the trials.

1           In conclusion, both drugs have  
2     indistinguishable efficacy and common safety  
3     problems that are cause for concern. But dapa has  
4     additional hazards not present with cana, which is  
5     on the market and available to patients. We agree  
6     with FDA's assessment that as a result of these  
7     updated analyses, the agency could not conclude,  
8     with any level of confidence, that the purported  
9     cardiovascular benefit associated with dapa  
10    outweighed the observed imbalance and specific  
11    malignancies or potential liver toxicity risks.  
12    Therefore, we urge this committee to vote against  
13    approval. Thank you.

14           DR. SMITH: Thank you. Will speaker  
15    number 2 please step up to the microphone.  
16    Identify yourself and any financial relationships  
17    you wish to disclose.

18           DR. RATNER: Good afternoon. My name is  
19    Robert Ratner. I have no conflicts of interest. I  
20    serve as the chief scientific and medical officer  
21    for the American Diabetes Association, which  
22    represents over 15,000 professional members and 26

1 million Americans with diabetes. Although the  
2 American Diabetes Association does not testify in  
3 support of individual products, we strongly support  
4 the need for further research and improved  
5 therapies for the treatment of diabetes as an unmet  
6 need.

7           Studies such as the United Kingdom  
8 Prospective Diabetes Study and the Kumamoto Study  
9 have demonstrated as much as a 40 percent reduction  
10 in severe eye, kidney and nerve complications for  
11 every 1 percent reduction in hemoglobin A1c.

12 That's why hemoglobin A1c is the surrogate marker  
13 of choice for this agency. It's important to keep  
14 in mind that the U.K. PDS took 17 years of  
15 follow-up to be able to observe those hard  
16 endpoints.

17           Despite our improvements in care, diabetes  
18 remains the most common cause of blindness in  
19 working-age adults and end-stage kidney disease in  
20 the United States. And although the Center for  
21 Disease Control and Prevention have reported  
22 improvements in hemoglobin A1c since 1999, over

1       40 percent of individuals with diabetes continue to  
2       have values in excess of 7 percent despite the use  
3       of currently approved FDA therapies.

4               It's equally important to remember that  
5       diabetes is a chronic disorder requiring daily  
6       attention to self-management over a lifetime with  
7       chronic complications occurring only after a decade  
8       or more. Treatment complexity and side effects,  
9       together with limited therapeutic targets,  
10      contribute to our inability to achieve treatment  
11      goals.

12             Therapies which simplify self-management and  
13      minimize side effects are imperative. Traditional  
14      therapies such as sulfonylureas and insulin  
15      aggravate the already problematic weight problem  
16      that most people with type 2 diabetes are trying to  
17      deal with. The ideal diabetes therapy would be  
18      that which is easy to take by mouth with little or  
19      no risk of hypoglycemia, no associated weight gain,  
20      and a favorable side effect profile.

21             The American Diabetes Association and the  
22      European Association for the Study of Diabetes

1 assembled a work group which produced a joint  
2 ADA-EASD treatment guidelines for type 2 diabetes  
3 in June of 2012 clearly delineating individualized  
4 treatment targets for patients, depending upon  
5 their life expectancy, disease duration,  
6 established comorbidities, resources and support  
7 systems, and their risk of hypoglycemia. For  
8 health adults, a reasonable glycemic goal might be  
9 the lowest hemoglobin A1c that does not cause  
10 hypoglycemia or weight gain.

11 Hypoglycemia has long been identified as the  
12 limiting factor in the treatment of hyperglycemia  
13 associated with diabetes. A recent work group  
14 defines iatrogenic hypoglycemia as all episodes of  
15 an abnormally low plasma glucose concentration that  
16 exposed the individual to potential harm.

17 A single threshold value for plasma glucose  
18 concentration that defines hypoglycemia cannot be  
19 assigned because glycemic thresholds for symptoms  
20 of hypoglycemia shift to lower plasma glucose  
21 concentrations after recent antecedent  
22 hypoglycemia, and to higher plasma glucose

1 concentrations in patients with poorly controlled  
2 diabetes and infrequent hypoglycemia. Because  
3 type 2 diabetes is much more prevalent than type 1  
4 diabetes, most episodes of hypoglycemia, including  
5 severe hypoglycemia, actually occur in people with  
6 type 2 diabetes.

7 There's growing evidence that patients with  
8 type 2 diabetes might be particularly vulnerable to  
9 adverse events associated with hypoglycemia. Over  
10 the last decade, three large-scale clinical trials  
11 have examined the effect of glucose lowering on  
12 cardiovascular events.

13 A total of 24,000 patients with high  
14 cardiovascular risk were randomized to either  
15 intensive glycemic control or standard therapy. In  
16 each, subjects randomized to the intensive arm  
17 experienced more episodes of hypoglycemia than did  
18 those randomized to the standard treatment arm.  
19 All three trials clearly demonstrated that an  
20 episode of hypoglycemia was associated with  
21 increased subsequent mortality.

22 The American Diabetes Association strives to

1 improve the lives of individuals with diabetes and  
2 those affected by it. Promoting glycemic control  
3 to minimize the risk of microvascular  
4 complications, such as retinopathy, kidney disease,  
5 and neuropathy, must be tempered the side effects.

6 DR. SMITH: Thank you. Will speaker  
7 number 3 please step up to the microphone. Identify  
8 yourself and any financial relationships you wish  
9 to disclose.

10 MR. DUNLAP: Good afternoon. My name is  
11 Bennet Dunlap. I have no relationship with the  
12 sponsor. My travel here today is at my own  
13 expense. That includes the expense of getting up  
14 at 4 a.m. and driving down from Philadelphia. I'm  
15 a diabetes advocate, a blogger. I've been a PCORI  
16 reviewer, and I recently created the Strip Safely  
17 campaign for meter accuracy.

18 I'm also a member of the Diabetes Advocates,  
19 which is a group of diabetes social media writers.  
20 Last time I was here, I absolutely slaughtered the  
21 name of canaga [ph], whatever the heck it's called,  
22 so I'm not even going to try today. But I'm really

1 encouraged to see that nobody else is trying  
2 either.

3 Like 26 million other Americans, I live with  
4 diabetes. This morning someone spoke of unintended  
5 wisdom. We'll take wisdom any way you've got it,  
6 unintended or otherwise. Reading medical  
7 literature, I often feel that it projects that  
8 diabetes care is easy. Many of us have felt that  
9 it is not and found that it doesn't help when,  
10 despite our best efforts, we're labeled as  
11 non-compliant. And maybe the problem has to do  
12 with unrealistic expectations or maybe even  
13 imperfect medications or treatments.

14 What I'm certain about is while all of us  
15 with diabetes can benefit from similar diet and  
16 exercise improvement, there's no one size fits all  
17 approach to good diabetes medications. We need  
18 choices. We need to be able to talk with them,  
19 with our doctors, like Bob, and we need innovation,  
20 which brings me to the purpose of today's meeting.  
21 The question is, has this sponsor met the safety  
22 and efficacy requirements necessary to mark their



1 candidate drug and does it present potential value  
2 to some of us, not all of us, living with diabetes?

3 Broadly speaking, the class of SLG-2  
4 medication is an exciting opportunity for glucose  
5 regulation. It encompasses four things that we  
6 haven't seen before: improved glucose levels in  
7 our blood, weight loss instead of weight gain, less  
8 hypoglycemia, unless it's been used with insulin,  
9 and the ease that comes in taking a pill. And Bob  
10 just referred to a lot of us. Is it going to work  
11 for everybody? No. It may work for some of us.

12 Expanding the class -- I'm going to try  
13 it -- including dapagliflozin, increases choice.  
14 There's already one SLG-2 on the market. None of  
15 us can pronounce it. A second one would be  
16 positive for obvious benefits from competition,  
17 broader education efforts, and broader outreach.  
18 We all know third-party payers love to bid the  
19 pharma companies against each other. That would be  
20 a benefit for patients and payers.

21 As you consider the benefits of diabetes  
22 medication outcomes, I encourage you to look at the

1 endpoints that create success in patients' daily  
2 lives in addition to the endpoints of lowering A1c,  
3 avoiding cancer, and CV risks. Look to endpoints  
4 that we can see and feel in our daily efforts to be  
5 compliant, medications that show less weight gain,  
6 or even weight loss, less hypoglycemia, and can  
7 help with the psychosocial struggle that we deal  
8 with everyday, 24/7, 365.

9 The safety issues raised earlier -- at the  
10 earlier hearing for this drug -- were quite  
11 concerning, and many of us in this social media  
12 community were put back by the cancer risks.  
13 Nobody wants to trade better blood sugar for  
14 cancer.

15 I appreciate the scrutiny that the agency  
16 and the sponsor have given to the issues raised,  
17 but I'm particularly interested in this morning's  
18 presentation on the bladder risk, and look forward  
19 to the detailed explanation. And I hope that you  
20 people can make it something that I as a patient  
21 understand.

22 Dr. Wilding pointed out that we need better

1 treatments. As a patient, I worry about regulation  
2 that may inhibit those regulations. I think it's  
3 important that what constitutes an effective study  
4 needs to be resolved before the study starts, not  
5 here in an advisory meeting. SLT-2s have become a  
6 potential new option for some patients guided with  
7 their healthcare team. We found them  
8 useful -- some of us have found them useful.

9 In closing, diabetes is self-care. As  
10 patients, we see our doctors just a few times a  
11 year, maybe for a combined total of an hour or two,  
12 if we're lucky. That leaves us on our own,  
13 responsible for our own self-care the other 8,758  
14 hours in a year. We could use a hand seeing  
15 success in that.

16 Thank you very much for your evaluations. I  
17 look forward to your detailed conversations on the  
18 cancer risks.

19 DR. SMITH: Thank you. Will speaker number  
20 4 please step up to the microphone? Identify  
21 yourself and any financial relationships you wish  
22 to disclose.

1 DR. ZUCKERMAN: I'm Dr. Diana Zuckerman.  
2 I'm president of the Cancer Prevention and  
3 Treatment Fund, and our center is dedicated to  
4 improving the health of adults and children. And  
5 we do that by conducting research and scrutinizing  
6 research, and then explaining the results to health  
7 professionals, to patients, and to the general  
8 public. And our nonprofit organization does not  
9 accept money from pharmaceutical companies, so I  
10 have no conflicts of interest.

11 Today I'm speaking from my perspective as  
12 someone trained in epidemiology at Yale Medical  
13 School. I was also on the faculty at Vassar and  
14 Yale and did research at Harvard, and was a fellow  
15 at the Center for Bioethics at the University of  
16 Pennsylvania.

17 So I'm putting together all those  
18 perspectives and also with input from an expert on  
19 our staff who was at the National Cancer Institute  
20 before she worked for us. But I'm also speaking as  
21 someone who has close family members with diabetes,  
22 including one relative who died from diabetes. So

1 I'm really speaking as a scientist but also with  
2 that additional perspective.

3 So obviously, FDA always has to balance the  
4 risks and benefits, so I'm going to first talk  
5 about the benefits, and then I'm going to talk  
6 about the risks.

7 How well does this drug work? The results  
8 indicate that dapa is not effective for patients  
9 with moderate to severe renal impairment. And as  
10 we all know, about 20 to 40 percent of diabetes  
11 patients do have compromised renal function, so  
12 that's a real issue. These drugs do not have to  
13 work for everybody in order to be beneficial, but  
14 it's always a problem when there's a very large  
15 group who can be harmed by a new drug.

16 As you've already heard today, dapa does not  
17 provide significant improvement over currently  
18 available drugs. Glipizide was superior in the  
19 short term and equally comparable to dapa at  
20 52 weeks.

21 So in the context of these modest benefits,  
22 very limited benefits and not particularly related

1 to health outcomes, what are the risks? And that's  
2 what I'm going to focus on.

3 FDA stated that the animal studies that were  
4 conducted could not rule out the risk of bladder  
5 cancer, and we completely agree. And I want to  
6 talk about that a little bit. Experiments done  
7 using cell lines and tumor models, when the tumor  
8 models are not implanted in the bladder of the  
9 animal, cannot answer questions about the risks to  
10 humans, because in humans, the changes in bladder,  
11 microenvironment, or urine flow may be most  
12 relevant to carcinogenesis.

13 So FDA has already suggested the use of what  
14 an appropriate animal model would be, specifically  
15 a chemically-induced rodent bladder cancer model.  
16 And for some reason, the companies have not  
17 conducted that kind of study. That's the kind of  
18 study that could tell us what's going on with  
19 bladder cancer without necessarily studying it  
20 anymore on humans.

21 So until those animal studies are done, dapa  
22 must be considered a possible cause of bladder

1 cancer. And since other effective diabetes drugs  
2 are already on the market, and those drugs are in  
3 fact more effective for more patients, bladder  
4 cancer, it seems to me and to our center, is an  
5 unacceptable risk.

6 But bladder cancer isn't the only risk. So  
7 what about breast cancer? That's been kind of  
8 dismissed by the FDA, and we disagree completely.  
9 The FDA gave several reasons. They said that the  
10 short treatment time prior to onset was reason not  
11 to think that the breast cancer was related to the  
12 drug; also, the decline in incidence risk ratio  
13 over time, and the fact that the breast cancers  
14 were estrogen-receptor positive.

15 So let's start with the short treatment time  
16 before onset. All of us know cancer takes time to  
17 develop. And normally, when you see cancer  
18 developing quickly after taking a drug, you assume  
19 it doesn't mean anything. This happened by chance.  
20 That's usually the assumption. But assuming that  
21 or hoping that's true is not the same as knowing  
22 it's true. And in fact, we have increasing

1 evidence that this is not always true.

2 The most dramatic example has to do with  
3 hormone replacement therapy. When the  
4 prescriptions for hormone replacement therapy  
5 dropped dramatically, the incidence of breast  
6 cancer in this country also dropped dramatically  
7 for the first time. And people thought, well, this  
8 couldn't be related. This is much too quick.

9 The prescriptions just got reduced recently,  
10 and suddenly the rates of cancer are going down.  
11 That doesn't make sense. But those rates of cancer  
12 stayed low -- lower I should say -- and the experts  
13 in the field now all agree that it was related to  
14 the hormone treatment and that the impact was much  
15 faster than it was expected, even though breast  
16 cancer can be a very slow-growing cancer or a  
17 faster growing cancer. But still it could be  
18 stimulated by the hormones that these women were  
19 taking.

20 We challenge the other two assumptions about  
21 breast cancer as well. We think that the hormone  
22 receptor status of the breast cancer is irrelevant



1 to the question because we don't have any idea how  
2 dapa might be causing or stimulating or being  
3 related to breast cancer. It's unknown. It's  
4 entirely possible that dapa could act in multiple  
5 biological pathways, including hormone receptor  
6 signaling or in a biological pathway that is common  
7 to breast cancer regardless of the hormone receptor  
8 status.

9 Similarly, the long-term biological  
10 responses to this drug and the potential feedback  
11 mechanisms in breast tissue are also unknown. And  
12 so the decline and the incidence risk ratio over  
13 time doesn't mean that the drug is safe because the  
14 body could be responding differently to the drug  
15 over a period of time.

16 So I'm not saying that this drug definitely  
17 is causing breast cancer. I'm saying we don't  
18 know, and we can't assume that it doesn't, that it  
19 doesn't cause it directly or indirectly or  
20 contribute to it in some way.

21 There are other safety issues, and you've  
22 heard about renal failure and renal impairment.

1 And the data clearly show an increase in renal  
2 failure and renal impairment. Also at two  
3 different doses, the dapa patients had elevated LDL  
4 levels while the placebo patients did not. And so  
5 again, this increase raises concerns that any  
6 potential cardiovascular benefit cannot justify  
7 these additional risks.

8 I want to say a couple of more things in the  
9 time remaining. One is the lack of diversity in  
10 the studies that have been done. This hasn't  
11 really been discussed at all. In the total sample  
12 of all the studies, less than 4 percent of the  
13 patients were African American, and yet 13 percent  
14 of African Americans have type 2 diabetes. They  
15 should have been tested if the intent for this drug  
16 is to get it approved for all Americans, not just  
17 for white Americans.

18 But I have to say that given the risks of  
19 cancer, it's very hard to say, oh, should we now  
20 study more African Americans. I think it does  
21 clearly raise ethical issues, and that's where my  
22 bioethics training really comes in to wonder

1       whether we should be doing that, and certainly that  
2       would be a reason to do the rodent studies that are  
3       really necessary.

4               In conclusion, I just want to talk about  
5       what are the implications of approval of a drug  
6       like this that has unknown but potentially very  
7       frightening risks and what seemed to be very modest  
8       benefits, and in fact not as good as other drugs on  
9       the market.

10              I know that there's a lot of desire to have  
11       a range of drugs because some drugs will be better  
12       for some patients, and some drugs will be better  
13       for other patients, and it's good to have those  
14       choices. But the reality is, when a drug is  
15       approved, a new drug is approved, it gets out  
16       there, and patients are often not given the  
17       information they need to make a good choice, and  
18       they're really relying on their doctors who may  
19       also not have all the information they need to help  
20       their patients make the safest choice.

21              I think that most of you on the panel are  
22       physicians, and I am sure that when you make

1 decisions for patients or talk to patients about  
2 their options, you definitely give them the best  
3 possible information. But unfortunately, many  
4 physicians out there in the real world are not as  
5 knowledgeable as you are.

6 So while I sympathize with the company's  
7 desire to get this new drug on the market, I say  
8 that the animal studies, the proper studies, need  
9 to be done first. And until that happens, I do not  
10 believe it would be ethical to approve this new  
11 drug. The risks are too great. Thank you.

12 **Clarifying Questions (continued)**

13 DR. SMITH: Thank you. And thanks to all of  
14 the open public hearing speakers. The open public  
15 hearing portion of this meeting has now concluded,  
16 and we will no longer take comments from the  
17 audience. 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  
20 well as the public comments.

21 So we will now begin the panel discussion  
22 portion of the meeting. Although this portion is

1 open to public observers, public attendees may not  
2 participate except at the specific request of the  
3 panel. What we're going to do structurally is  
4 we're going to start out asking the sponsor to  
5 share some of the data that were put together in  
6 response to specific questions this morning. We'll  
7 do that first.

8 DR. LIST: Yes. There were several  
9 questions put to us both verbally here and then  
10 also in email from Dr. Hiatt, and we'll attempt to  
11 address these briefly each.

12 First question had to do with cystoscopy and  
13 did we capture cystoscopy in the phase 3 program.  
14 We did not capture cystoscopy as a -- we did not do  
15 routine collection of cystoscopy events in the  
16 phase 3 program. We did not have an a priori  
17 hypothesis of bladder cancer. We will be capturing  
18 all workups of hematuria in the DECLARE study. And  
19 so cystoscopies will be gathered there.

20 The second question had to do with changes  
21 in bacterial or fungal flora in patients treated  
22 with dapagliflozin. We don't have any data on

1 fungal flora, although I would note that the  
2 incidence of fungal infections is much higher in  
3 females than males. Bladder cancers are per mL in  
4 males. And where we do have anecdotal data from  
5 the infections, cultured data, it's generally  
6 candidal species, nothing unusual. In fact,  
7 candida is found in up to 30 percent of patients  
8 with diabetes as a commensal.

9 We do have data on bacteria, however. We  
10 did a substudy of around 400 patients in study 19.  
11 And in this substudy, it was equally distributed  
12 between dapagliflozin 10 milligrams and placebo.  
13 We were looking to see if there was an effect of  
14 dapagliflozin on asymptomatic bacteriuria.

15 So in this substudy, we measured -- we did  
16 urine cultures at various time points on all of the  
17 patients in the substudy, at baseline, at 8 weeks,  
18 at 24 weeks. And what we saw, first of all, is we  
19 didn't see a change in the carriage rate of  
20 asymptomatic bacteriuria. So it was about the same  
21 percent, dapa and placebo, and at various time  
22 points.

1           We also within that study characterized the  
2 bacteria scene when there were greater than 100,000  
3 colony counts per mL. And if I can have slide  
4 NS-4, please? This shows dapa on the left column  
5 and placebo on the right column for people who had  
6 baseline -- who had positive cultures at week 8.  
7 And these are people who were baseline negative, so  
8 to see the acquisition of urinary tract pathogens  
9 or flora, if you will.

10           What we see here is nothing that's all that  
11 unusual or markedly different in nature between  
12 dapagliflozin and placebo. I'm sorry. These are  
13 people who are positive at baseline, and then were  
14 positive at week 8. I said that backwards.

15           We also have data on people who were  
16 negative at baseline and then positive at week 8.  
17 So what we're showing you here are positive  
18 baseline, positive at week 8.

19           If I can have slide NS-2, please? These are  
20 people who are negative at baseline, positive at  
21 week 8, and showing what was cultured out of their  
22 urine. And again, similar proportions between dapa

1       and placebo acquire urinary organisms. And when  
2       you look at the organisms, they're not unusual  
3       organisms and not markedly different between dapa  
4       and control. Our assessment of this is that it  
5       doesn't seem to be any evidence of a change in  
6       microbiological flora in patients treated with  
7       dapa.

8               The next question or series of --

9               DR. SMITH: Okay. Dr. Wilson, I think you  
10       had asked about that. Anymore questions or  
11       comments related to that set of data?

12              DR. W. WILSON: The other thing that I had  
13       asked is that within the biopsies of the patients  
14       that had transitional cell carcinoma, was there  
15       anything unusual in terms of inflammation that one  
16       wouldn't otherwise find within a biopsy of a  
17       similar tumor that was taken out of somebody that  
18       wasn't exposed to this drug?

19              DR. LIST: There's nothing noted in the  
20       biopsy reports that we've received that was notably  
21       different from what you would expect in that  
22       population.



1 DR. W. WILSON: Okay. Thank you.

2 DR. SMITH: We can go on to the next one,  
3 then.

4 DR. LIST: The next series of questions had  
5 to do with missingness of data and accounting for  
6 that. And I'd like to ask Dr. Henry from our  
7 biostatistics group to address those series of  
8 questions.

9 DR. HENRY: David Henry, biostatistics,  
10 Bristol-Myers Squibb. Dr. Packer, you asked for an  
11 analysis of the placebo-controlled trials. I do  
12 not have the sensitivity analyses for the  
13 placebo-controlled trials here. I have one for all  
14 controlled trials. As a note, about 13 percent of  
15 the patients would be removed from the analysis if  
16 we were doing one with the placebo-controlled only.  
17 So we would not expect the results to differ  
18 drastically.

19 DR. PACKER: I'm sorry. That's interesting,  
20 but how do you know that the results would not  
21 differ? You don't know what happened to those 13  
22 percent. I don't understand the basis of your

1 conclusion.

2 DR. HENRY: Okay.

3 DR. PACKER: You don't have the data, so you  
4 don't know?

5 DR. HENRY: We can tell you about the  
6 studies where -- that were the active-controlled  
7 studies.

8 DR. PACKER: The active-controlled studies  
9 are really hard because I'm not certain what the  
10 control agent does. So that's why I asked about  
11 the placebo-controlled trials. Most of your data  
12 are the placebo-controlled trials. And if  
13 you -- and I just want to make sure that we focus  
14 the question correctly because the guidance  
15 document, with its wisdom, says that sponsors  
16 should conduct a proper meta-analysis and should  
17 obtain sufficient endpoints to allow for a  
18 meaningful estimate of risks. It doesn't say how  
19 many endpoints.

20 The program should include patients at high  
21 risk for cardiovascular events, such as patients  
22 with advanced disease, elderly patients, patients

1 with some degree of renal impairment.

2 We know from previous work that if you're  
3 going to look for a signal, the last place you want  
4 to look for it is in patients who won't have it.  
5 So healthy people who don't have events are not a  
6 particularly sensitive population to rule out a  
7 risk.

8 So I just want to make sure that I  
9 understand, you have -- in patients who had a  
10 history of cardiovascular disease, in the  
11 placebo-controlled trials, there were 1856 patients  
12 randomized to dapa and 1358 patients randomized to  
13 placebo. You don't know how many missing patients  
14 there are in that database?

15 DR. HENRY: We can -- we have done most of  
16 our work with sensitivity analyses upon the primary  
17 database, which has included the active-controlled  
18 studies as part of it.

19 DR. PACKER: When you say sensitivity  
20 analysis, can you tell me what you did?

21 DR. HENRY: Sure. May I see slide 42-9,  
22 please? Let me start by nothing that in the design

1 of the study, patients were followed for  
2 cardiovascular events up to one month after  
3 discontinuation from treatment. Follow-up was not  
4 available beyond one month after treatment  
5 discontinuation.

6 DR. PACKER: Can I just ask you to pause?  
7 We heard from FDA that because there were two  
8 sponsors, one sponsor followed people for longer  
9 than 30 days. That wasn't true?

10 DR. HENRY: I can't speak for another  
11 sponsor, but we followed them for 30 days after the  
12 end of treatment.

13 DR. PACKER: Can we clarify for the whole  
14 database whether AstraZeneca followed people for  
15 longer than 30 days, since this is supposed to be  
16 sort of a unified presentation?

17 DR. HENRY: I believe when the FDA was  
18 referring to companies, they were referring to  
19 Canna and Johnson & Johnson. Or are you  
20 referring -- you're referring to us? Just a  
21 second.

22 DR. LIST: Maybe I can clarify. There are

1       some slight differences in the databases between  
2       Bristol-Myers and AstraZeneca. Bristol-Myers  
3       followed these events, and all serious adverse  
4       events, up to 30 days after the last dose of study  
5       drug.

6               In the AstraZeneca studies, there was  
7       routinely a follow-up visit at 3 weeks, and their  
8       events were followed up routinely up to 3 weeks or  
9       that follow-up visit after last dose of study drug.  
10       In both cases, if an event was reported before  
11       database closure, before the database was locked,  
12       it was adjudicated and incorporated into the  
13       cardiovascular analyses.

14              DR. PACKER: But what I think what I hear is  
15       that for all practical purposes, there was no  
16       systematic attempt to follow people for events  
17       beyond 3 or 4 weeks after discontinuation of the  
18       drug. Is that fair?

19              DR. LIST: That's correct. That's fair.

20              DR. PACKER: I'm sorry. Please.

21              DR. HENRY: So if we consider the maximum  
22       possible follow-up, which would be of all subjects

1 continued on study through short-term and through  
2 long-term phases, there would be 19 percent of that  
3 total maximum follow-up that is not available on  
4 the dapagliflozin arm due to discontinuation from  
5 treatment, and 24 percent on the control arm.

6 To stress test the impact of the missing  
7 follow-up data, we imputed unfavorable event rates  
8 to the dapagliflozin arm and very favorable rates  
9 to the control arm. For the control arm, we  
10 assumed that there were no additional events. For  
11 the dapagliflozin arm, we considered variable  
12 multiples of the on-treatment rates.

13 The first column gives the on-treatment rate  
14 that we're imputing for the off-treatment patients.  
15 If we go down to 3 times the multiple of the  
16 on-treatment rate, we have a confidence interval  
17 where the upper bound is below the FDA  
18 1.8 criteria. So even with very pessimistic  
19 assumptions with regard to events, no events on  
20 control and a rate that's approximately 3 times the  
21 on-treatment rate, we meet the criterion that the  
22 FDA has specified. And this is MACE by the way.

1 DR. PACKER: And I do want to focus on MACE,  
2 and I really appreciate you doing that because I  
3 really think that's the endpoint that should be the  
4 area of focus. But could you clarify one thing?  
5 Because I'm puzzled.

6 The FDA has focused on studies 18 and 19 and  
7 focused on MACE events. In the MACE events in  
8 Studies 18 and 19 -- and the reason that you  
9 focused on the 18 and 19 was they had the entry  
10 criteria for the history of cardiovascular disease.  
11 There were 61 MACE events with a hazard ratio of  
12 1.1. In your whole placebo-controlled population,  
13 which includes 18 and 19, you had 95 MACE events  
14 with a hazard ratio of .82.

15 The difference between 61 and 95 is 34  
16 events in the trials that didn't specifically  
17 enroll people with cardiovascular risk. But the  
18 hazard ratio of .8 for the entire group versus 1.1  
19 for 18 to 19 means that you must have had an  
20 incredible benefit in patients who were in the  
21 other trials. Is that correct?

22 DR. LIST: The hazard ratio in the other

1 trials -- that is the high CV risk patients outside  
2 of 18 and 19 -- was around .5. Dr. Sabatine has  
3 closely reviewed these data, and perhaps he could  
4 shed some more light on how these two  
5 subgroups -- of the overall high-risk sub group  
6 compared to each other.

7 Dr. Sabatine?

8 DR. SABATINE: Thank you, Dr. List.

9 Good afternoon. My name is Marc Sabatine.  
10 I'm a cardiologist at Brigham and Women's Hospital  
11 and Hartford Medical School, and also a clinical  
12 trial as the chair of the TIMI study group. I am a  
13 paid consultant. My institution has received  
14 research grant support from the applicant, but I  
15 have no financial interest in the results of these  
16 deliberations.

17 So there have been important questions asked  
18 about the various subgroups. I think one theme to  
19 keep in mind, certainly if you look at subgroups,  
20 is any apparent heterogeneity is hard to replicate  
21 for those. And usually, the most reliable estimate  
22 is from the overall totality of the data.



1       Certainly, there's interest in looking for those  
2       individuals who might be at higher risk. And I  
3       think then if one were to take that approach, it  
4       should be a risk-based approach.

5               I would underscore that trials 18 and 19 are  
6       a convenient administrative way to pull out trials,  
7       which certainly did have patients with a history of  
8       cardiovascular disease, but they're not all the  
9       patients with cardiovascular disease. So I would  
10      in fact argue that -- I would look at first those  
11      with CV history. If we could just refresh your  
12      memory by bringing up the core slide for  
13      adjudicated CV outcomes, 115, please.

14             So let's start for the primary endpoint,  
15      which is what was agreed upon at the beginning, but  
16      certainly I don't disagree with the emphasis on  
17      MACE as well. So we start with .79 for the  
18      primary. If we look in a clinical or biologic  
19      subgroup defined by history of CV disease at .81,  
20      very similar. We do the same analysis for MACE.  
21      It goes .77 to .80.

22             Now, I would say another way to look at the

1 data -- then could be 18 and 19 -- if you were to  
2 pull those -- I think we have the slide for the  
3 primary endpoint --

4 DR. PACKER: Just for the sake of time, I  
5 understand your -- I just want to make sure that I  
6 understand what the answer to my question was. In  
7 18 and 19, the risk ratio was 1.1.

8 DR. SABATINE: That's correct. You can pull  
9 up slide 117.

10 DR. PACKER: In all other trials for people  
11 at cardiovascular risk, it was 0.5

12 DR. SABATINE: That's right.

13 DR. PACKER: That's different.

14 DR. SABATINE: And that difference is  
15 defined -- I think -- those numbers are different.  
16 But that's defined administratively --

17 DR. PACKER: No, no. Those numbers are very  
18 different. I don't need an interaction p value to  
19 tell me that those numbers are different. I'm not  
20 asking whether they're statistically significantly  
21 different. I'm asking -- I have concluded that .5  
22 is different than 1.1 You agree?

1 DR. SABATINE: I would view the data through  
2 a different lens for the -- and let me share that  
3 with you.

4 If we can pull up a slide looking at the  
5 event rate -- I think 47 and 24 -- so this gets at  
6 the notion of is there a difference to your query  
7 between the patients who were in 18 and 19 versus  
8 those who had a history of CV disease, but just by  
9 chance didn't happen to be enrolled in trials 18  
10 and 19. And I would draw your attention, then, to  
11 the highlighted event rates in the control arm.  
12 And you'll see that it is -- for MACE, 2.6 percent  
13 in 18 and 19, and 3.5 for those with a history of  
14 CV disease, but not in 18 or 19.

15 DR. PACKER: I'm sorry. Those are events  
16 over what period of time?

17 DR. SABATINE: Over the duration of  
18 follow-up, which on average I believe was about a  
19 year or so; on average. It depends on the  
20 particular -- 18 and 19, longer.

21 DR. PACKER: What I see there is something  
22 even a little bit more scary, which is it's 1.11

1 compared to 0.41. It's not even 0.5; 0.41.

2 DR. SABATINE: Yes.

3 DR. PACKER: So I would conclude that for  
4 whatever reason, the estimate that I get for MACE  
5 inputs from 18 and 19, looks meaningfully different  
6 than for other patients at increase with a history  
7 of cardiovascular disease. I don't see how you can  
8 come up with a different conclusion.

9 DR. SABATINE: If we have a slide that looks  
10 at patients by disease state for MACE, I think 44  
11 or 41, if we can pull that up. So this is a  
12 different way to look at it, where we're not  
13 dividing patients by what trial they happen to be  
14 in, but by the characteristics of the patients.

15 Here, we've divided the overall cohort into  
16 three different bins. The first row has those  
17 patients who have no history of CV disease. You go  
18 one row down, those are patients with a history of  
19 CV disease but without heart events, without a  
20 history of MI, cerebral vascular accident, or  
21 stroke, or peripheral vascular disease. And then  
22 the third row is those patients with a history of

1 MI, stroke, or PVD.

2 I have to say when I look at these data, I  
3 don't see any trend towards a differential effect  
4 based on risk or disease state.

5 DR. PACKER: Let me suggest when you are  
6 showing me 18 events in one subgroup analysis of a  
7 subgroup analysis, and 39 in another, and 77 in  
8 another, I will conclude that that data is  
9 insufficient to tell me very much. The number of  
10 events, it's too sparse. You're trying to provide  
11 reassurance when the amount of data is not there.  
12 And you're also doing this on censored data. So  
13 I'm not telling you that you have a problem. I'm  
14 telling you that you don't know enough about  
15 whether you have a problem or not.

16 DR. SABATINE: I would point out that the  
17 data for MACE in trials 18 and 19 had, as you  
18 pointed out, 61 events, right? So here we have  
19 MACE in a population of individuals with MI,  
20 stroke, or PVD, and now we have 77 events.

21 DR. PACKER: Maybe I should ask the question  
22 in the following way. If you knew that the whole

1       idea of doing a meta-analysis was to get a reliable  
2       point estimate in confidence intervals, especially  
3       the upper bound of the confidence interval, why  
4       didn't you follow patients for the planned duration  
5       of double-blind therapy as it would be required for  
6       a proper meta-analysis?

7               DR. SABATINE: I can let Dr. List comment on  
8       the --

9               DR. LIST: The trials were carried  
10       out -- first of all, the phase 2 and phase 3  
11       program were already started at the time the FDA  
12       guidance came out. The trials were carried out in  
13       the manner in which we've traditionally carried  
14       out -- diabetes trials, in the manner that they're  
15       carried out by other sponsors.

16               Understanding that, that is a limitation of  
17       the data. And it is also a limitation when you try  
18       to break this into smaller subgroups, and you see  
19       numeric differences. But I think it's important to  
20       step back and remember the intention here, we've  
21       got this dynamic tension, if you will, between  
22       looking at the safety within a clinical trials

1 program design to test a drug for the treatment of  
2 diabetes and the ability to know about  
3 cardiovascular safety from the evidence coming from  
4 those trials.

5 DR. PACKER: I'm just going to add one  
6 thing, and then I'm going to close. See, the  
7 problem is that you sized this -- you didn't  
8 actually do a cardiovascular safety study. What  
9 you did was you did a diabetes study, and you tried  
10 to get cardiovascular safety. When you do a  
11 cardiovascular safety study, you follow people for  
12 the entire duration of double-blind therapy. And  
13 since you wanted to do cardiovascular safety, even  
14 if the trials were ongoing, you could have said  
15 we're going to follow people, even though the trial  
16 is ongoing, for events after 30 days. You could  
17 have said that.

18 So the problem is that I think what the FDA  
19 wants is, if you're going to assess cardiovascular  
20 safety, they want a cardiovascular safety study.  
21 They don't want a diabetes study where you sort of  
22 pick up some cardiovascular events. And the

1 difficulty here is that 18 and 19 are special not  
2 just because they were enriched for patients with  
3 cardiovascular disease, but they were your longest  
4 trials. And I would be in particular interested in  
5 knowing how much censoring there was in 18 and 19.

6 When you see a situation where the point  
7 estimate is 1.1 for the high-risk patients, 1.41  
8 for the high-risk patients in other studies, and  
9 the patients in other studies may have been  
10 followed for a shorter period of time and the  
11 patients in 18 and 19 were followed for a longer  
12 period of time, that difference gives me pause in  
13 terms of saying I know what the cardiovascular  
14 safety here is because you didn't really do a  
15 cardiovascular safety study.

16 DR. LIST: I just want to correct one minor  
17 misimpression. These are long studies, but they're  
18 not our longest study. We have a four-year study.  
19 We have other two-year data. And our intention is  
20 not to prove safety, but it's to rule out an  
21 unacceptable increase in risk. We have an ongoing  
22 cardiovascular study that will have the type of



1 follow-up that you are talking about with the  
2 specific intention of testing the hypothesis of  
3 cardiovascular safety --

4 DR. PACKER: Just to make the point. Just  
5 suppose you did a trial, just a trial, one study,  
6 and you found -- you enriched it for patient  
7 population. You had everyone who had  
8 cardiovascular disease. You followed people for  
9 the full duration of intended double-blind therapy.  
10 And you collected about 50 events, and you got a  
11 risk ratio of .5 with the upper bound at .8 or .9.

12 Would you conclude cardiovascular safety?  
13 Don't forget. The point estimate is in the right  
14 direction. The upper bound is less than 1. You  
15 have 50 events. Would you conclude cardiovascular  
16 safety? I'm not even saying benefit. Would you  
17 conclude cardiovascular safety?

18 DR. LIST: Well, again, that's not the  
19 situation here.

20 DR. PACKER: Well, no. But the guidance  
21 says that if the upper bound is less than 1.8, and  
22 it doesn't say on how many events, I want to know

1       whether you would conclude that based on 50 events  
2       instead of 122 events.

3               DR. LIST: I think we would look to an  
4       august body such as this to help us with that. But  
5       here we have 95 MACE events and 126 primary  
6       endpoint events.

7               DR. PACKER: So let me just make sure, that  
8       if you found that in 50 events, I would tell you  
9       that that was a totally uninformative finding. And  
10      I'm not certain there's a big difference between 50  
11      events and 122 events, especially when you have the  
12      issue of censoring.

13              So I'm not -- I don't want to fault you for  
14      doing what you've done. I'm just saying that it is  
15      inadequate for me to assess cardiovascular safety.  
16      If you want to do cardiovascular safety, you  
17      actually do it as a cardiovascular safety study.  
18      The number of events is meaningful. The type of  
19      events is meaningful. And there shouldn't be  
20      censoring.

21              DR. SMITH: Okay. I think we're going to  
22      have discussion on this point.

1 Dr. Brittain?

2 DR. BRITTAIN: Yes. I just wanted to follow  
3 up a little bit. In terms of the concern about  
4 whether 18 and 19 had different follow-up than the  
5 other studies, different lengths of follow-up, do  
6 you have Kaplan-Meier or anything that can give us  
7 information about the comparisons at one year, at  
8 two years, that kind of thing?

9 DR. LIST: Yes. We do have Kaplan-Meier,  
10 and I believe the FDA also presented one. And that  
11 was one of Dr. Hiatt's questions, do we agree with  
12 the FDA's Kaplan-Meier.

13 DR. BRITTAIN: I guess relevant to that, is  
14 18 -- I mean, the results from 18 and 19. I don't  
15 know if that can be separated from that.

16 DR. LIST: Yes. We have the separated  
17 results also. First, slide 45-2, this is the  
18 Kaplan-Meier for the primary endpoint for studies  
19 18 and 19. The curves do cross over each other a  
20 couple of times, as pointed out by FDA.

21 Now, would you like to see the individual  
22 results for 18 and for 19, or more questions on

1       this?

2               DR. BRITTAIN: No. I guess the concern was  
3       about the other studies who have high-risk patients  
4       that didn't -- that seemed to have a different  
5       result. And I don't know if you would have any  
6       information relevant to that in terms of the  
7       timing.

8               DR. LIST: We don't have that broken down by  
9       study. We simply have it as -- as Dr. Sabatine  
10      showed you, we've looked at the 18 half if you  
11      will, and the non-18 half. But what we can show  
12      you is for study 18 and study 19, the endpoints,  
13      individual.

14              Okay.

15              DR. SMITH: What I would suggest we do  
16      now -- you said no, right? I understood you  
17      correctly?

18              Dr. Brittain, you didn't want to see them  
19      separately?

20              DR. BRITTAIN: Yes. If other people do.

21              DR. SMITH: So what I'm suggesting we do is  
22      that we go through the request that Dr. Hiatt had,

1       which are we'll bring some more data for us to look  
2       at. And then if there's more discussion that  
3       people feel should come before we get to the  
4       discussion questions, okay, remembering that the  
5       first discussion question is focused on  
6       cardiovascular -- and I'd like to state the  
7       question in front of us before we have a lot more  
8       discussion about cardiovascular stuff.

9               So I'll restate that in a minute after  
10       Dr. Hiatt's. If you could provide the questions  
11       that Dr. Hiatt asked, or I will if you need me to.  
12       I think I gave you a copy.

13              DR. LIST: Yes. So the first one is, "Is  
14       there a constant proportional hazard rate on MACE  
15       events? Sponsor's slide 120 suggests no early  
16       risk, but FDA figure 2, page 148, slide 31, which  
17       is confined to 18 and 19, suggests an early risk."  
18       And I'd like to have Dr. Henry address this  
19       question.

20              DR. HENRY: David Henry, Bristol-Myers  
21       Squibb, biostatistics. May I see slide 42-4,  
22       please?

1           We examined proportional hazards in a number  
2 of different ways, both for the primary endpoint  
3 for MACE, looking at all patients, looking at just  
4 those with a history of CVD, and those in studies  
5 18 and 19. We didn't see significant p values  
6 indicating non-proportional hazards in any of those  
7 cases.

8           I would caution here that I believe the  
9 interest in this question was to see whether this  
10 contributed to the discussion of the first month.  
11 And it's important that we keep in mind that that  
12 first month is a very small fraction of the overall  
13 time period. And as a result, any non-proportional  
14 hazards in that first month, if there were any,  
15 it's unlikely that it would come out in a global  
16 test over the whole period here.

17           In the FDA summary, they look at that first  
18 month and estimate the hazard ratio within that  
19 first month. And if you look at the confidence  
20 interval on that, it's a very wide confidence  
21 interval. It goes from the point estimate down to  
22 a fifth of the point estimate, and up to 5 times

1 the point estimate. And this was in all patients,  
2 not just 18 and 19 only.

3 So any comparison that one makes between  
4 that first one month and the rest of the study  
5 would have a large amount of variability because of  
6 the great variability in that first month. We have  
7 the issue here that though in this study, there  
8 does seem to be a slightly higher, I believe it was  
9 a 2.6 relative risk, the amount of variability  
10 attached to that is very large.

11 DR. SMITH: Dr. Hiatt, I assume you're  
12 there. Do you have any further question or comment  
13 in regard to these data?

14 DR. HIATT: So I think looking at the slide  
15 that the sponsor prepared just a minute ago on the  
16 event rates between groups for trials 18 and 19,  
17 that they agreed with the FDA assessment, that  
18 those event rates were crossing -- going from early  
19 to late in the study?

20 DR. LIST: Yes. We agree that those event  
21 rates are crossing. I think the issue is that it's  
22 a sparse amount of data.

1 DR. HIATT: Okay. And then I did have a  
2 separate question. And that was to look at the  
3 MACE events in the placebo-controlled trials,  
4 eliminating the active-controlled trials. Any  
5 comment on that?

6 DR. LIST: Yes. Can we have the  
7 placebo-controlled experience, please? We have  
8 that. We've done that analysis by dose. We  
9 haven't done it pooling all the doses together.

10 DR. HIATT: As you're preparing that, just a  
11 simple question. And that is, what is your assumed  
12 MACE event rate in your cardiovascular outcome  
13 trial?

14 DR. LIST: I'd like to have Dr. Sabatine  
15 from the TIMI group answer that one, and then we'll  
16 get back to the MACE events in the placebo trials.

17 DR. SABATINE: Marc Sabatine, Brigham and  
18 Women's. If you could pull up the design slide for  
19 DECLARE from the main deck, please? Yes, that's  
20 131.

21 So just in response, Dr. Hiatt, to your  
22 question, just underscore it is an event-driven



1 trial, so we will accrue at least 1390 events,  
2 regardless of what the event rate is. We projected  
3 the per annum rate for MACE should be around  
4 2.1 percent or so.

5 DR. HIATT: Okay. And it's probably too  
6 early in the study to know what that event rate  
7 actually is.

8 DR. SABATINE: That's exactly right.

9 DR. HIATT: But I do note that the median  
10 follow-up is quite long. Have you accounted for  
11 potential dropouts or patients discontinuing  
12 therapy? And what are you going to do if the event  
13 rate is substantially lower than your projections?

14 DR. SABATINE: So we do follow that, and we  
15 put in a lot of work for retention for patients.  
16 Certainly, we'd like patients to stay on drug as  
17 long as tolerated. And I think in terms of  
18 follow-up, our goal is to follow up all patients  
19 carefully. In general for the TIMI trials, the  
20 rate of lost to follow-up tends to be less than .1  
21 percent per year. So they should have a small  
22 impact. Now, if the event rate is lower than

1       anticipated, we would then follow patients for  
2       longer.

3               DR. HIATT: Which presents a challenge if  
4       you're trying to keep patients adherent to study  
5       drug.

6               DR. PACKER: Not really, because you're  
7       following the patients even if they come off drug.

8               DR. SABATINE: That is correct.

9               DR. PACKER: So the patients will accrue  
10      events whether or not they're on drug or not. The  
11      only problem -- if there is one, and I'm not saying  
12      that there is one -- is it hurts you if you're  
13      looking for superiority. It helps you if you're  
14      looking for neutrality.

15              DR. SABATINE: Right. And so I think  
16      that's -- just to respond to that comment, I think  
17      that's an important point. For superiority, that's  
18      absolutely right, that if patients are off drug,  
19      it's hard to show a benefit. The converse, which  
20      you also quite appropriately underscored, is that  
21      when you're doing an analysis for safety or  
22      non-inferiority, some would argue, in fact, the

1 most conservative approach is only to follow  
2 patients when they're on drug. Adding time when  
3 they're off drug just gives you time that likely  
4 would bias to the null. Just something to keep in  
5 mind for the follow-up for existing phase 2b/3.

6 DR. SMITH: I would like to ask if people  
7 wish to speak, if you would please wait until I  
8 authorize that. If you have a question that is  
9 immediately related to the topic under discussion,  
10 absolutely let me know that also. But I want to  
11 try to keep this on track that way. So if you've  
12 got more that's immediately related, that's good.

13 DR. LIST: Getting back to the other  
14 question that Dr. Hiatt had, if I could have slide  
15 46-4, please? Here we have the endpoints broken  
16 down for the phase 2b/3 program by dose for dapa  
17 against placebo. So this doesn't have the active  
18 comparator trials in it. And we see MACE is the  
19 third one in each of these three categories. And  
20 we see the MACE endpoint with point estimates at  
21 10 milligrams as .9, 5 milligrams as .39, and  
22 2.5 milligrams as .7.

1 Does that answer your question, Dr. Hiatt?

2 DR. HIATT: Yes. Thank you.

3 DR. SMITH: So again, I want to allow a  
4 little more time. I want to get to these questions  
5 soon, but I want to make sure that people had a  
6 chance to ask information related questions before  
7 we do that. And I'm going to go back to some  
8 people who may not even remember that they were on  
9 the list this morning.

10 Dr. Savage, you had wanted to ask a question  
11 a couple of hours ago. Do you still -- I apologize  
12 for waiting, but I told you I'd remember everybody  
13 who had one. Okay. That's fair enough.

14 Dr. Fojo, I think you had a comment or  
15 question also. And again, we all know what the  
16 discussion questions are, so I'd ask not to discuss  
17 the discussion questions. This is an information  
18 related or things of that nature.

19 DR. FOJO: Yes. I actually had two  
20 questions, and one of them has been bandied about  
21 here with regards to the -- can you show slide 119  
22 and 120 from the core? 119 quickly, and then go to

1 120. So this says primary endpoint MACE plus UA.

2 Where is 18 and 19 in this? Is it included  
3 or not?

4 DR. LIST: Eighteen and 19 are included in  
5 this, yes.

6 DR. FOJO: Included in this. And then can  
7 you clarify for us, 18 and 19, are they that much  
8 longer than everybody else put together in terms of  
9 the follow-up?

10 DR. LIST: Actually, the follow-up in 18 and  
11 19 is a little bit complicated. They were  
12 originally designed as one-year studies, and the  
13 average duration here is about a year, a little  
14 over a year. They were then amended while they  
15 were ongoing to extend it to two years. About  
16 two-thirds of the patients had completed the study,  
17 so it didn't go into that second year extension.  
18 So they kind of drop down and go to a full two  
19 years.

20 We only have one study that's longer than  
21 two years, and that's a four-year study. And  
22 that's why you see fairly small numbers as we go

1 out beyond two years in our Kaplan-Meier plots.  
2 But we have other studies that go to two years, for  
3 instance, our add-on to insulin study, which was a  
4 comparably large study.

5 DR. FOJO: Okay. Then just go to 120, just  
6 in the interest of time. And I'm not quite  
7 sure -- there was a suggestion that short studies  
8 might give you a better result than the longer  
9 studies, the .41, .51 versus 1.11. I wonder if  
10 this sort of data, though, speaks against that  
11 because it's not ideal, but you're not seeing a  
12 whole lot of change over this interval about your  
13 patient.

14 DR. PACKER: Just to address the point, as a  
15 general rule, if you take low-risk patients that  
16 are followed for 12 weeks, and you include them in  
17 the meta-analysis together with high-risk patients,  
18 who are followed for two years, that creates a  
19 delusional effect of the point estimate.

20 DR. FOJO: Right, but this is being analyzed  
21 for all patients at that point in time. It's out  
22 to 24 months.

1 DR. LIST: This is all patients. We also  
2 have this for the prespecified, high-risk subgroup  
3 if you'd like to see that.

4 DR. FOJO: Okay. Sure.

5 DR. LIST: Can we have the hazard rate for  
6 the high CV risk subgroup, please? Slide 45-10,  
7 please. We see a similar pattern.

8 DR. FOJO: Okay. All right. And then the  
9 last question that I had is on core 54. It comes  
10 back to the questions that were being asked about  
11 censoring and so forth. Are all these patients  
12 being told -- why their numbers are dropping low?

13 DR. SMITH: I'd like Dr. Parikh to address  
14 the question.

15 DR. PARIKH: Yes. So this efficacy analysis  
16 reflects the patients who are on the study up to  
17 the two-year time point. Now this was one of the  
18 trials which did not have a rescue criteria because  
19 these patients were already on metformin, and then  
20 there was active comparisons between dapagliflozin  
21 and sulfonylureas. So most investigators wanted  
22 these patients to move on to insulin. So we had to

1       discontinue patients if they met prespecified  
2       glycemic criteria.

3               So the most common reason why we didn't have  
4       patients was actually captured in the previous  
5       slide, core slide 53, which is the same  
6       trial -- well, we show you -- if you could bring up  
7       core 53, please? So this was the main reason why  
8       we didn't have some of the patients at the two-year  
9       time point, which is the reason for prespecific  
10      glycemic criteria. They had to be discontinued.  
11      And we lost more patients on glipizide than on  
12      dapagliflozin here.

13              In other trials, we do have rescue, and we  
14      did do analysis, including those rescue patients.  
15      So we have more patients.

16              DR. FOJO: Okay. But go back to 54. So  
17      that maybe explains why the numbers dropped off.  
18      But why is the weight stabilizing, and why doesn't  
19      it continue to drop off? You know, if you do a  
20      calculation of how much glucose you're spilling,  
21      how many calories you get per glucose, you're right  
22      at the beginning right on target with regards to



1       your kilograms loss in terms of how much glucose  
2       you're spilling, and then all of a sudden, it  
3       plateaus out. Why?

4               DR. LIST: This is a question that has come  
5       up because you continue to have the same glucose  
6       here. We do have an expert in obesity in diabetes,  
7       Dr. Wilding, and perhaps he has some thoughts, if  
8       that would be okay with the chairman.

9               DR. WILDING: Yes. Thank you very much.  
10       John Wilding. I think the reason why we see this  
11       plateauing of body weight loss, if you look at any  
12       weight loss intervention, whether you use a drug,  
13       or diet, or exercise, or even bariatric surgery,  
14       eventually you reach a plateau because as you lose  
15       weight, your lean body mass falls, your energy  
16       expenditure falls, and eventually you reach a new  
17       steady state. I think that's the main reason why  
18       we see a plateau here.

19               It is possible and there is some preclinical  
20       data that suggests that there may be some small  
21       compensator increase in food intake, and that may  
22       be why that the absolute weight loss isn't perhaps

1 as much as we might expect to see based on the  
2 amount of energy that's being lost in the urine.  
3 And that's an issue that we're hoping to address in  
4 a small investigational study in the near future.

5 DR. FOJO: Okay. I'm good.

6 DR. SMITH: Dr. Brittain, you had a question  
7 or comment.

8 DR. BRITTAIN: I just wanted to quickly  
9 follow up on the slides where we saw the  
10 Kaplan-Meier. Do you have anything -- do you have  
11 a Kaplan-Meier slide that has either standard  
12 errors or confidence intervals?

13 DR. LIST: We do not have one with  
14 confidence intervals.

15 DR. BRITTAIN: It would have been useful to  
16 see how much precision there is early on versus  
17 late.

18 DR. SMITH: Dr. Wilson?

19 DR. W. WILSON: I wanted to follow up with  
20 the FDA, especially after we had this discussion,  
21 about what the intent of the FDA was in asking for  
22 these cardiovascular risk studies. And I just

1        wanted to have a clarification for myself and the  
2        committee. It was my understanding that not the  
3        current ongoing study, but up to this point, it was  
4        the FDA's desire to rule out the presence of  
5        increased cardiac disease -- I shouldn't say rule  
6        out, but to determine whether or not there was any  
7        signal for it as opposed to rule it out, which is a  
8        very different kind of study.

9                DR. GUETTIER: I'm going to start off, and  
10       then I'll let other people weigh in. So the 2008  
11       guidance happened after our public meeting. And it  
12       was decided at that meeting that, number one,  
13       diabetes drugs were not getting evaluated for  
14       cardiovascular risk prior to 2008. So we were  
15       relying on preclinical signals, on imbalances in  
16       programs that were really not designed to evaluate  
17       cardiovascular risk adequately.

18               The guidance basically defines how to  
19       evaluate cardiovascular risk very broadly and  
20       generally in a diabetes program. So the applicant  
21       followed a path that was agreed upon by the FDA,  
22       which was actually to combine their diabetes trials

1       into a prespecified meta-analysis that was reviewed  
2       within FDA and agreed upon.

3               I think we're hoping to get from this  
4       particular advisory committee is there's a lot of  
5       ways that you can actually evaluate cardiovascular  
6       risk. And as we're learning from programs that  
7       have undergone this process, there are different  
8       ways to evaluate cardiovascular risk, and we are  
9       wondering what people think about just the issues  
10      that are being discussed today.

11             DR. W. WILSON: So it was my understanding  
12      in the FDA's presentation that the assessment of  
13      cardiovascular, to the extent it's been done, that  
14      FDA and the sponsor both have a similar  
15      interpretation. Is that correct?

16             DR. GUETTIER: Are you referring to the  
17      prespecified meta-analysis?

18             DR. W. WILSON: Yes.

19             DR. GUETTIER: That would be correct.

20             DR. W. WILSON: Thank you.

21             DR. SMITH: Dr. Lewis, you had a question  
22      before. Did you still have that?

1 DR. LEWIS: Yes. I just wanted to clarify  
2 because it will help inform me when I think about  
3 this. So it would seem to me that one of the  
4 things that you're saying is that we should look at  
5 the largest number of events, that if you look  
6 across all the studies, the 135, 145, or 122,  
7 depending on how you cut it, events should inform  
8 us more than the events in just 18 or 19, which is  
9 a smaller number.

10 I also would just say as an aside -- and I  
11 may want you to answer that -- that I don't think  
12 that there are any low-risk cardiovascular patients  
13 in these trials. I consider diabetes and the 60-70  
14 percent of them having hypertension as very  
15 significant cardiovascular risks. I realize that  
16 there are degrees.

17 DR. PACKER: The best way I can answer is it  
18 is degrees. And so if someone has a history of  
19 cardiovascular disease, they're going to be at a  
20 higher risk than someone without a history of  
21 cardiovascular disease, although the 40-year-old  
22 who doesn't have a history of cardiovascular, who's

1       only had diabetes for a year, is not at low risk,  
2       but they're at much lower risk.

3               The more -- what you need to think of is the  
4       reason this study of high-risk patients is twofold,  
5       one, they have events. And two is, in general,  
6       higher risk patients will be a more sensitive  
7       substrate for a toxic effect of the drug. So  
8       that's the reason that we focus on high-risk  
9       patients. It's very hard to look for risk in  
10      people who don't experience events.

11             DR. SMITH: Dr. Fojo?

12             DR. FOJO: Just in this discussion, I'm a  
13      little concerned because we're ending up  
14      looking -- actually, there aren't that many events,  
15      really, at the end of the day. And maybe they can  
16      just show the slide again. That was the second  
17      slide to Dr. Hiatt's answer that had the 10, the 5,  
18      and the 2 and a half for the MACE. It had the half  
19      ratios for that. And there in fact, you see going  
20      from 10 to 5, there's a dramatic change, one that  
21      you would say I don't need any data. I know the  
22      difference between --

1 DR. PACKER: No, no.

2 DR. FOJO: -- 90 and .39.

3 DR. PACKER: No. I don't want to be  
4 misunderstood.

5 DR. FOJO: No, no. But I'm just saying  
6 that --

7 DR. PACKER: When you have sparse events --

8 DR. FOJO: Right.

9 DR. PACKER: -- you have very little  
10 information. You have unreliable estimates. P  
11 values and confidence intervals don't help you very  
12 much. So what we have here is a few number of  
13 events. A meaningful number of events is 1300  
14 events, which is what they're going for in DECLARE.  
15 That's a meaningful number of events.

16 DR. FOJO: Correct. But I'm not quite sure  
17 that 18/19 versus everything else, we're at that  
18 level of meaningful events, which is what I think  
19 you were saying. That's not the way --

20 DR. PACKER: No --

21 DR. FOJO: I'm just trying to get clarity.

22 DR. PACKER: That's the whole point. The

1 whole point is 1.1 looks different than .41. It  
2 looks different. Neither estimate is reliable --

3 DR. FOJO: Correct.

4 DR. PACKER: -- because the number of events  
5 is small.

6 DR. FOJO: Okay.

7 DR. PACKER: Does that help you?

8 DR. FOJO: Yes, because .9 and .39 looks  
9 different, but neither one of those is reliable.

10 DR. PACKER: Right. It's similar to if one  
11 person flips a coin at this end of the table, and  
12 it comes out 73 heads/tails, and on this side of  
13 the table, it comes out 3/7, which easily could  
14 happen. Are those two coins different from each  
15 other. And the answer is I don't know.

16 DR. FOJO: Right. Okay.

17 DR. SMITH: Dr. Peter Wilson?

18 DR. W. WILSON: To build a little bit on  
19 what Dr. Packer's been saying, I've wondered -- I  
20 haven't seen sex-specific data, especially in sort  
21 of the longer half of the distribution of people at  
22 risk for first events. So I was especially



1       wondering what fraction of the users in the trials  
2       that have been reported here are women under  
3       55 years of age. Because they're just not going to  
4       have events, has been my experience.

5               DR. LIST: If I can have slide 46-1, please?  
6       So we don't have sex broken down by age. What we  
7       can tell you is this is the various prespecified  
8       subgroups across the meta-analysis. But when you  
9       look at gender here or sex, the second row, we  
10      don't see a difference between males and females,  
11      about half of the women in the program, as well as  
12      half of the men, were under the -- the mean and  
13      median ages were similar, which is around I believe  
14      52 or so.

15             DR. SMITH: Thank you. I want to move to  
16      discussion questions, but I actually have one more  
17      informational question that I would like to ask.  
18      And I'm going to change the topic, and I'm going to  
19      be back to talking about bladder cancer just  
20      briefly. And I'm looking for some advice from the  
21      FDA or alternatively perhaps from Dr. Bajorin.

22             My understanding is that there are a number

1 of meta-analyses, including some recent ones, which  
2 show an increased risk of bladder cancer in  
3 diabetes; and it's modest, but an increased risk.  
4 This is not my area, so I stand to be corrected if  
5 the BALANCE study says no.

6 But my question is, other than that, your  
7 thoughts about how this may color the way we think  
8 about the data that we've seen on bladder cancer.  
9 It certainly has influence on the in vitro data.  
10 It has influence on animal models -- I didn't ask  
11 earlier because we were filled with questions  
12 here -- but also particularly related to human  
13 studies.

14 So the question is, do you agree that  
15 there's a background of data supporting increased  
16 bladder cancer risk, modest so it may be, in  
17 diabetes? And secondly, how should that color how  
18 we think about these data?

19 DR. PUCINO: Yes, there is a meta-analysis  
20 that suggests there is an increase. It's  
21 statistical, but the question is how much weight of  
22 evidence does that apply to the circumstance in

1       this case. I don't know if our consultant Dr. Ning  
2       is here. He also referenced that in his consult,  
3       if he's available.

4               DR. NING: I'm Dr. Ning. I'm a medical  
5       oncologist and medical officer working at the  
6       Office of Oncology Products. I evaluated the  
7       bladder cancer risk associated with dapa for this  
8       NDA. Regarding the risk of bladder cancer in  
9       patients with diabetes, I mean, if that is the  
10      case -- first I think that there isn't a contest  
11      [indiscernible] about whether bladder cancer risk  
12      increases in patients with diabetes. If that is  
13      the case, you would see an increased number of  
14      bladder cancer diagnosed in patients not receiving  
15      dapagliflozin.

16             So here I think the key question to me when  
17      I evaluated was whether there was a considerable  
18      imbalance in the diagnosis of bladder cancer  
19      between patients receiving dapa and the patients  
20      not receiving dapa. So I think this imbalance is  
21      clear. I don't know whether anyone does not  
22      disagree with that observed imbalance.

1 DR. SMITH: Dr. Wilson, did you have a  
2 comment relevant to this point?

3 DR. W. WILSON: I did. To the extent that  
4 there may be a signal of increased bladder cancer  
5 and diabetes, is this independent of other risk  
6 factors for bladder cancer, like smoking?

7 DR. NING: Dr. Wilson, I think that in this  
8 patient population, I think we always have  
9 confounding factors. I feel that attribution of  
10 dapa basically could not be totally ruled out.

11 DR. W. WILSON: That's not my question. My  
12 question is in reference to Dr. Smith's question,  
13 which was does diabetes have an underlying  
14 increased risk of bladder cancer. I believe I  
15 heard that there was some meta-analyses that  
16 suggested that. And so my question is, is that  
17 independent of other risk factors for bladder  
18 cancer?

19 DR. SMITH: My understanding is yes, from  
20 those meta-analyses.

21 DR. NING: Yes. Some meta-analyses suggest.  
22 Some meta-analyses basically does not suggest. So

1 I think the data basically is kind of conflicted.

2 DR. SMITH: Dr. Lewis, did you -- sorry.

3 DR. W. WILSON: Does anyone who knows about  
4 this meta-analyses know that these are independent?

5 DR. LEWIS: So I looked them up, and there  
6 were two that I found that said it was an  
7 independent risk factor. They're epidemiologic  
8 studies, so they are what they are. But they said  
9 it was an independent factor.

10 Can I -- go ahead.

11 DR. HAMPP: I just want to speak to this.  
12 Christian Hampp, epidemiologist, Office of  
13 Surveillance and Epidemiology. The meta-analysis  
14 contains several studies. Some of them had  
15 adjustment for smoking; others did not. They had a  
16 subgroup analyses for different studies they  
17 included, and studies that did adjust for smoking  
18 had an increased risk for diabetes. So diabetes,  
19 an increased for bladder cancer adjusted for  
20 smoking.

21 DR. LEWIS: I asked the question of the FDA.  
22 Although Dr. Wolf's colleague did an elegant

1 presentation, I'm not used to getting my answers  
2 and data from them. But they said that there were  
3 5 cases in the cana group of bladder cancer and 4  
4 in the control group. Can you verify that?

5 DR. PUCINO: Yes. Actually, from the  
6 initial application and the initial background  
7 package for the canagliflozin NDA, they looked at  
8 the 100- and 300-milligram approved doses and the  
9 all non-cana group. In the cana 100-milligram dose  
10 cohort, there were 3,139 patients. In the  
11 30-milligram, there were 3,509. In the all  
12 non-cana group, there were 3,640. Actual bladder  
13 cancer cases in the 100-milligram dose, there were  
14 2 events for an incidence of .06 percent.

15 In the cana 300-milligram dose group, there  
16 were 3 for an incidence of 0.09. And then for the  
17 oral non-cana group, there were 4 events for an  
18 incidence of 0.11. So this ultimately ends up with  
19 an incident rate per 1,000 patient-years for the  
20 three groups respectively, 0.44, 0.63, and 0.84.

21 DR. LEWIS: Thank you.

22 DR. SMITH: So before we go to discussion

1       questions --

2               DR. PACKER: I just have one question about  
3       bladder cancer. Can I just ask to -- how reliable  
4       is it for -- if you look at bladder cancers, and  
5       you see an imbalance, for oncologists, expert  
6       oncologists, to review the individual histories and  
7       try to determine whether something is causal or  
8       not? I know that you've done that. I just want to  
9       know whether that method is reliable.

10              DR. LIST: I guess I would have to ask our  
11       bladder oncologists who've done these reviews of  
12       the reliability of this methodology. I will say  
13       the whole intention here is like your analogy with  
14       two coins. We flipped some coins, and we've got  
15       one coin saying more bladder cancers and one saying  
16       less renal cancers, for example. So we're  
17       interrogating the data to understand are these two  
18       coins the same or different.

19              Dr. Bajorin?

20              DR. BAJORIN: Dean Bajorin, Sloan-Kettering  
21       Institute. I think the issue reverts back to the  
22       small number of cases, which I've heard multiple

1 times this morning. And when you have a small  
2 number of cases, and even someone doing a p value,  
3 of a nominal p value, the central question is to go  
4 back to the patient cases and ask does this really  
5 make clinical sense or not. And so that's what I  
6 did. We actually went back to each and every case,  
7 and you ask questions like we would ask in the  
8 clinic. And that is, are there other predisposing  
9 factors or do you see the same elements that you  
10 would see in general clinical practice.

11 What I saw was multiple episodes of  
12 hematuria, patients with gross hematuria who are on  
13 aspirin. I see a number of patients in whom the TA  
14 tumors, which take years to develop, had hematuria  
15 before we see them. And then for the patients with  
16 the advance disease -- and I have a patient at  
17 30 days who has anorexia and weight loss -- I know  
18 that that patient has preexisting disease. So I  
19 think that that's really the issue, is small  
20 numbers, to go back and ask the --

21 DR. PACKER: So if I understand the  
22 methodology, if you look at the individual patients



1 and there is a short duration from the onset of the  
2 new treatment to the diagnosis of cancer, or if you  
3 can find alternative explanations, that makes you  
4 feel that there is not a causal relationship. Is  
5 that fair?

6 DR. BAJORIN: Yes, that is fair. This is a  
7 disease that develops over years, not over several  
8 months.

9 DR. PACKER: Just in response to that, I  
10 just would like to get your comment. There was a  
11 study that was carried out with pioglitazone called  
12 PROACTIVE. It's also a diabetes drug, which had an  
13 increased risk of bladder cancer. The individuals  
14 who looked at the PROACTIVE study found that there  
15 was an imbalance in PROACTIVE of 14 cases in the  
16 pio group versus 5 in the placebo group, not  
17 statistically significant, but a risk ratio of  
18 about 2.4.

19 What the sponsor did was they asked an  
20 expert urologist, to a group of people, to do a  
21 review. And they took 11 of the 14 cases and threw  
22 them out because they had a short incubation

1 period. And they took 6 cases and threw them out  
2 because it was an additional -- there were already  
3 additional risk factors. So at the end, they  
4 concluded, based on this methodology, that  
5 pioglitazone was not associated with the increased  
6 risk of bladder cancer. But it is.

7 DR. BAJORIN: I think it's something very  
8 important to point out here. That's a very good  
9 example of how do you find bladder cancer risk, not  
10 from the clinical oncologist review, but the fact  
11 that you have a drug there that alters gene  
12 expression so mechanistically, it may make sense.  
13 It had a preclinical signal for bladder cancer, so  
14 it failed in the models that we have.

15 Again, these models detect all known human  
16 bladder carcinogens. And then they had both the  
17 clinical studies and the pharmacoepidemiology  
18 studies, which we are currently conducting in  
19 Europe, all pointed in the same direction.

20 DR. PACKER: And that's totally correct.  
21 All I'm saying is that they also went through a  
22 methodology of urological oncology review, which

1 dismissed the imbalance. And that methodology did  
2 not turn out to be a reliable approach to  
3 determining causation.

4 DR. BAJORIN: Yes. I think we can't hang  
5 our hat on any single piece of information,  
6 including the imbalance because it's such sparse  
7 data. And that's why we have to look at the  
8 totality of evidence.

9 DR. SMITH: Dr. Peter Wilson?

10 DR. P. WILSON: So I'm starting to digest  
11 what was up and present in 2011, and thinking if I  
12 were going to be using this medication in a trial  
13 from 2011 onward, who would go into the studies.  
14 And that has an effect on what's going on today and  
15 what might go on in the future.

16 So if I have a diabetic patient for whom I  
17 need to lower Alc more, and I then screen him, it  
18 sounds like I should be screening him if I'm going  
19 to use this drug, based on 2011 data at hand, for  
20 hematuria. I don't know whether I can use the dip  
21 stick in the clinic or I should get a fasting  
22 overnight specimen to screen him. I'm going to

1 have a couple of questions, as you're going to see  
2 here. They're going to go to both sides, both to  
3 the FDA and to the sponsor.

4 If he's on aspirin, I have some concern why  
5 he might also have hematuria. And if he has a  
6 recent urinary tract infection, which many of my  
7 diabetic patients have, I have to get some other  
8 reasons. And if he has hematuria, I'm concerned  
9 about having him potentially take placebo or dapa  
10 to be in a trial. And has that been addressed  
11 since 2011 to help sort out, because most of these  
12 patients who develop bladder cancer -- and some of  
13 them for sure at the screening point -- had  
14 hematuria. So help me out as a clinician. I'm  
15 wearing my clinical hat here.

16 DR. LIST: So I'll try to address this.  
17 There are several points here, and let me know if I  
18 miss something here. The first thing is how do you  
19 screen -- how does screening hematuria work when  
20 you're looking for bladder cancer. I think that  
21 was the first underlying question. Typically, spot  
22 screening and dip stick itself, finding trade

1 hematuria is appropriate screening. And in fact,  
2 if you see trace or greater hematuria on more than  
3 one sample in a male, that is, by standard of care,  
4 cause for a workup for bladder cancer, and that's  
5 regardless of dapagliflozin. So if you see  
6 hematuria, bladder cancer should be thought of.

7 With respect to how we're conducting trials  
8 going forward with the information we have, I think  
9 the DECLARE study is an example of how we now -- we  
10 did our original trials without any hypothesis of  
11 bladder cancer. Now we're doing a safety test  
12 within the DECLARE study. So what we do there is  
13 we do screen for hematuria, and we make sure that  
14 the patients who have hematuria have standard of  
15 care workups, and then they enter the trial. And  
16 that's just asking for standard of care, not  
17 something special.

18 I think the other piece of data, it's a very  
19 limited piece of data but may help to speak to this  
20 as well. We saw 11 bladder cancers throughout the  
21 program. Again, 10 were on dapa with twice as many  
22 patients on dapa. We did have 5 patients in the

1       dapa group who had had a history of bladder cancer.  
2       None of those 5 had bladder cancer during the  
3       study. So we don't see any evidence for dapa  
4       causing recurrence or exacerbation of preexisting  
5       bladder tumors.

6               DR. SMITH: Is that a good enough -- that's  
7       enough --

8               DR. P. WILSON: So if a person has  
9       hematuria, he needs to be worked up. Is one screen  
10      enough, and how much of a workup? They mentioned  
11      just usual care, but should it go beyond usual  
12      care?

13              DR. LIST: Perhaps Dr. Bajorin, who knows  
14      much more about this than I do, could comment.

15              DR. BAJORIN: So the standard of care that's  
16      recommended, both in U.S. and by the European  
17      Urologic Association, is that it should be a  
18      complete evaluation, which includes imaging and  
19      does include cystoscopy if one does not identify a  
20      specific risk, and it concludes cytology as well.  
21      So it's actually more comprehensive than what I  
22      think is usually done in the clinic.

1 DR. P. WILSON: As a follow-up, if  
2 somebody's in a trial or using this medication  
3 versus placebo, should they get a follow-up?  
4 Should there be a six-month or a one-year follow-up  
5 for a longer study?

6 DR. LIST: We do have -- so we've been in  
7 all of our trials checking urine blood at every  
8 visit, and we will have routine follow-ups of urine  
9 blood in the DECLARE study for the duration of the  
10 study.

11 DR. SMITH: So I would like to move to  
12 discussion.

13 Yes, Dr. Lewis?

14 DR. LEWIS: If I could just address that  
15 point. I want to remind you that depending on what  
16 study you look at, anywhere from 8 maybe to 12, 15  
17 percent of diabetics have hematuria who do not have  
18 bladder cancer. It's from the diabetes. It's also  
19 not -- it's enriched in people who have diabetic  
20 nephropathy. As a nephrologist, we all the time  
21 see people who have chronic hematuria from IGA or  
22 whatever, diabetes. There is no answer to the

1 question how often you evaluate them because they,  
2 like anyone else, 10 years later could get bladder  
3 cancer.

4 So I think there is no answer to that  
5 question. I mean, I don't think -- there could be  
6 an answer, but there isn't one in the literature.

7 **Questions to the Committee and Discussion**

8 DR. SMITH: So I would like to move us on to  
9 the discussion questions, and I'm getting nods.  
10 While we're getting the first question up, if  
11 everyone would look at their microphone. If your  
12 light is on, please turn it off, Dr. Pucino.

13 (Laughter.)

14 DR. SMITH: I tried not to mention your  
15 name.

16 So the first of these is a discussion  
17 question. And I'll read the question, and then  
18 we'll open it up to the floor for the response of  
19 people and thoughts about this question. So I'll  
20 start by reading it.

21 Cardiovascular Risk Evaluation. Based on  
22 the information provided in the briefing package



1       and the presentations at today's meeting, please  
2       address the following with regard to the  
3       cardiovascular risk assessment for dapagliflozin.  
4       Comment on which data -- i.e., overall population,  
5       enriched population -- best inform the  
6       cardiovascular risk associated with dapa use, and  
7       discuss the weight you place on the evidence  
8       provided by the subgroup of patients specifically  
9       recruited on the basis of established  
10      cardiovascular disease in trials 18 and 19.

11               B. Discuss whether you believe the updated  
12      cardiovascular risk data derived from trials 18 and  
13      19 are consistent with the overall findings  
14      reported for the pool of 21 clinical trials.

15               C. Discuss the clinical importance you  
16      place on the observed changes in blood pressure,  
17      weight, glycemic control, and lipid parameters in  
18      informing overall cardiovascular risk of dapa.

19               D. Discuss additional concerns, if any, you  
20      may have with regard to dapa and cardiovascular  
21      risk.

22               So I'll open up the floor. Dr. Brittain.

1 DR. BRITTAIN: Well, as I see it,  
2 conclusions don't change a whole lot, depending on  
3 which analysis I'm looking at, especially if the  
4 standard really is 1.8. It seems like no matter  
5 how you look at the data -- I agree the censoring's  
6 an issue, and we can talk about that in a moment.  
7 But it seems like whether you're looking at the 18  
8 and 19 or whether you're looking at the whole  
9 population, the upper bounds of the confidence  
10 intervals are so much lower than 1.8.

11 So if that's really the question, I'm not  
12 too concerned -- I mean, I'm not really -- not  
13 concerned at all. I think all of this is an  
14 initial assessment of whether there's a safety  
15 signal, and I don't see -- in terms of  
16 cardiovascular risk -- any indication of a safety  
17 signal.

18 I do agree that the censoring is important,  
19 that it would be better to following everybody to  
20 the full duration. But I thought the sensitivity  
21 analysis that was shown was useful. Obviously,  
22 you're not going to get as good data to assess the

1       cardiovascular risk from these studies as you will  
2       in the study that they've just started.

3               I guess I like confidence intervals a lot  
4       better than Dr. Packer seems to. I'm not quite  
5       sure -- I guess we'll hear more about why he  
6       doesn't like them or finds them misleading.

7               So I'm not really sure I understood that  
8       concern. I mean, I agree that the different  
9       studies that have different follow-up periods could  
10      be -- the different distributions of follow-ups in  
11      different studies could lead to somewhat misleading  
12      results or hard to reconcile results. But again,  
13      overall, the main conclusion is that if anything,  
14      the reason to be somewhat optimistic. And I don't  
15      really see any concern that there's any risk at  
16      approaching 1.8.

17              In terms of the question that was raised  
18      about the fact that the high-risk patients who were  
19      outside of study 18 and 19 had a much lower hazard  
20      ratio than the patients in 18 and 19 who were also  
21      high risk, I think it's certainly possible that  
22      that's just statistical noise, and isn't wasn't

1 clearly hugely different from each other in terms  
2 of the variability around the point estimates.

3 Again, it's possible there were differences  
4 in those studies in terms of what other drugs they  
5 were talking. Each study had different designs.  
6 So there could be reasons why there were somewhat  
7 different results. But that in itself I guess I'd  
8 not find worrisome. Again, overall, I feel I'm not  
9 concern by these results.

10 DR. SMITH: Thank you. Other comments on  
11 this? Dr. Peter Wilson. This is my fault. It  
12 would be helpful if you would state your name  
13 before you make your comments, everyone for the  
14 record.

15 DR. P. WILSON: Peter Wilson. I share that  
16 overall impression for the atherosclerotic  
17 cardiovascular risk factors and for obesity, which  
18 is underlying it. There's favorable signal for  
19 obesity, favorable for blood pressure, minimally  
20 unfavorable for LDL or atherogenic lipids. And  
21 that seems to hold for canagliflozin as well, so  
22 it's a class effect. But I think also -- and I

1       would guess that this -- I won't guess, as I don't  
2       know. But it appears to balance out; at least  
3       these are minor effects for each of these.

4               The other two things I think that is  
5       important to add on top of what Dr. Brittain -- are  
6       fluid effects, electrolytes, and potential  
7       arrhythmia because we're talking cardiovascular  
8       safety. And there does not appear to be a fluid  
9       retention issue as seen with some other  
10      hypoglycemic agents. In fact, it may go the other  
11      direction or it's neutral to favorable.

12             Arrhythmia, we have no information to  
13      suggest electrolyte abnormalities are arrhythmias.  
14      So overall it looks fairly neutral. The most  
15      helpful data has been the increased event data from  
16      18 and 19. And as Dr. Packer has mentioned, the  
17      very favorable signal for first events may be a  
18      mixture of people at fairly low risk and fairly low  
19      numbers. So we have less confidence, in fact how  
20      strong -- or how confident we are those estimates  
21      are. But the overall effect does not appear to be  
22      adverse, even with adding 18 and 19.

1 DR. SMITH: Other comments? Dr. Thomas?

2 DR. THOMAS: Abraham Thomas. I  
3 think -- everyone's said points that I would have  
4 mentioned. What I wanted to just highlight is, I  
5 think the real question is not is this drug safe in  
6 terms of for continued use, but is it safe enough  
7 to go to market if it's approved for other reasons.  
8 And I think they've met that criteria in terms of  
9 the point estimates and their confidence intervals.

10 The process is not to limit the development  
11 of diabetes drugs or to slow down the progression  
12 to market, but to eliminate those that are clearly  
13 not safe at an early stage of development. So I  
14 think these are not enough events to be reliable in  
15 terms of powering this study to say that it's fine,  
16 but I would think that if there were enough events,  
17 to be powered to enough events with the data they  
18 have, if they had those types of estimates, you  
19 probably wouldn't need to do another study. They  
20 would have met the criteria quite easily. They  
21 just don't have enough events, and that's why the  
22 long-term trial will be needed to answer that.

1           The one thing I would suggest, I think we  
2       would gain much more information -- many of these  
3       trials that have been done so far usually do the  
4       diabetes study, agent/placebo, and then whatever  
5       the general practice is in the area. I think we  
6       would gain a lot more if there was standardization  
7       of other treatments such as the use of statins,  
8       especially with the one concern that we have.  
9       Everything's going in the right direction, weight  
10      loss. Glucose is going down. Blood pressure's  
11      going down. The only thing that's going in the  
12      wrong direction is LDL.

13           So if there was some standardization in the  
14      trials to look at LDL by making sure statins are  
15      used at a certain level or guidance, I think that  
16      would be more informative once we get the results  
17      of these trials, beyond the elimination of excess  
18      risk.

19           DR. SMITH: Dr. Hiatt?

20           DR. HIATT: A few technical difficulties.  
21      I'd like to comment on the first discussion point.  
22      I think [indiscernible] estimating cardiovascular

1 risks probably best made in the overall population,  
2 which is the most informative population. However,  
3 I do think that the other cardiovascular subgroups  
4 that were looked at did not show discrepant results  
5 as was seen for studies 18 and 19.

6 But 18 and 19 [audio gap] there may be  
7 cardiovascular risk, particularly early in  
8 treatment and also when that evaluation of risk is  
9 from the primary composite endpoint to the pure  
10 MACE endpoint. I also agree that there may be dose  
11 response so that the evidence for that is quite  
12 weak.

13 All this is definitive, but I think the  
14 signal persists for increased MACE risk probably in  
15 treatment. [Indiscernible] from the briefing  
16 document during the discussion, this does look  
17 similar to the canagliflozin discussion we had  
18 earlier in the year. Therefore, I think there is a  
19 cardiovascular risk signal. It's not well  
20 established in the overall results and may be  
21 confined to certain populations and certain times  
22 in dosing.



1           A cardiovascular outcome trial in this  
2       population as proposed will be conducted for many  
3       years to acquire a number of events. I'm concerned  
4       that rate may not be as high as originally  
5       specified. I'm also concerned that while retention  
6       may not be an issue, keeping patients on drugs,  
7       exposure to drug could be challenging.

8           Therefore, there are some risks that these  
9       questions may not fully answer in a cardiovascular  
10      outcome trial if that trial's not run to a  
11      successful completion. I'm not suggesting that  
12      will happen, but I just wanted to be careful to say  
13      that we could push all the definition of these  
14      risks into the trial that might give us that answer  
15      for many, many years. Thank you.

16           DR. SMITH: Dr. Wyndham Wilson.

17           DR. W. WILSON: So I just wanted to add my  
18      voice to the consensus that I at least hear  
19      beginning to form that there doesn't appear  
20      currently to be a significant signal of increased  
21      cardiac risk. I think the number of events, and  
22      therefore the sensitivity of your data, is coming

1 from FDA guidance. And I'm not sure that we're  
2 really here in a position to be able to say whether  
3 or not that guidance is correct or not.

4 However, I too am not that concerned when  
5 you look at the hazard ratio for the 18 and 19  
6 versus all cardiac patients simply because they  
7 aren't the same trials. And there could be other  
8 confounding factors that made the control arms more  
9 toxic in the all-cardiac risk groups.

10 Again, recognizing that it's not the MACE  
11 endpoint, but at least it's somewhat comforting to  
12 know that the hazard rate estimates for the primary  
13 endpoints, including all groups, really remained  
14 unchanged over time in the dapag group. And one  
15 would expect that if in fact this drug did increase  
16 cardiac problems, that you would begin to see an  
17 accrued risk over time, and we don't see that. In  
18 fact, the invert KM curves in core 119 actually  
19 shows that the control group begins to rise above  
20 the dapag group.

21 DR. SMITH: Dr. Packer?

22 DR. PACKER: I think if you were to ask me

1        what I know about the cardiovascular risk of this  
2        drug, I would say I don't know very much. The  
3        number of events is small. The fact that the point  
4        estimates are favorable to neutral is very  
5        reassuring. But the censoring gives me pause  
6        because we have missing data, and I really don't  
7        know what that missing data would have shown.

8                The appearance of the Kaplan-Meier curves,  
9        not particularly reassuring to me because most of  
10       the curves that separated the end is driven by two  
11       or three events. And what we're looking at is  
12       we're trying to define the future by looking at tea  
13       leaves, and we're not really good at that.

14               So if you ask me does this meet the criteria  
15       for the cardiovascular risk according to the  
16       guidance, the answer is, well, sort of. I would  
17       have liked not to see censoring. I would have  
18       liked to have more events. But, yeah, okay. Do I  
19       know that that means that this drug has established  
20       cardiovascular? The answer is no.

21               So all I would suggest is that  
22       cardiovascular issues not be an impediment to

1 approval but that the labeling should not give  
2 reassurance that we know a whole lot about the  
3 cardiovascular profile of this drug.

4 DR. SMITH: Ms. Hallare?

5 MS. HALLARE: Diana Hallare. I am concerned  
6 about the lack of diversity with regards to the  
7 study sample. And what I'm concerned about is  
8 that, as one of the audience mentioned -- for  
9 instance, Hispanic Americans and African Americans  
10 may have higher risks with cardiovascular and  
11 diabetes. And so what I'm wondering and what I'm  
12 concerned is that would data exacerbate the risk  
13 for cardiovascular outcomes.

14 I know there was a slide before with regard  
15 to the different countries where the data was  
16 tested. And for instance, Asia was more towards  
17 control. And I'm not sure whether the data from  
18 other countries justifies the diversity study.

19 DR. SMITH: Thank you. I concur for the  
20 most part with what I've heard from everyone. I  
21 want to comment a little more on letter C, where we  
22 heard some comments about blood pressure and lipid

1 parameters being minor and not particularly  
2 concerning, and perhaps offsetting changes.

3 I wanted to just make a comment about the  
4 weight loss. The weight loss is modest in degree,  
5 but I think it's important to consider that in  
6 actual patient effectiveness of utilization of  
7 drugs by patients, that even modest amounts of  
8 weight loss as compared to weight gain can really  
9 have substantial influence in clinical practice.

10 So in my practice experience, I not  
11 infrequently encountered difficulties persuading  
12 patients to take a given medication or continue a  
13 different medication. And perhaps I suspect they  
14 don't adhere very reliably, without telling me at  
15 times if it's accompanied by weight gain.  
16 Oppositely, a drug that results in weight loss has  
17 kind of a reinforcing quality that can have a spin  
18 over and greater adherence beyond just swallowing a  
19 pill or a capsule.

20 So even though that's a modest effect, I  
21 think it's significant in terms of how that might  
22 play out in actual utilization in clinical

1 practice, and that should be acknowledged.

2 Dr. Rasmussen?

3 DR. RASMUSSEN: I just want to add a few  
4 comments. I think the wording of the question,  
5 specifically this time around, not referencing the  
6 guidance from 2008 because the majority of this  
7 program was initiated prior to the implementation  
8 of that guidance.

9 So the program the sponsor has conducted has  
10 been with the purpose of demonstrating benefit in  
11 the relevant add-on indications and with very  
12 controlled comparator groups, whereas, in your  
13 usual cardiovascular study, you allow standard of  
14 care, which makes interpretation of benefit a bit  
15 more difficult.

16 To the benefit of our discussion, I think  
17 the events have been collected to a high standard  
18 with adjudication across the program, and a  
19 significant amount of events, which correspond to  
20 what I think we're going to see for most new  
21 diabetes drugs in the years to come around the 122  
22 events.

1           I just want to add one thing also because  
2       it's come up a couple of times regarding the  
3       demographics of the study population. And I'll  
4       just remind the panel that most sponsors today do  
5       complete global development, which means that you  
6       can't expect the total population to reflect the  
7       U.S. population in terms of Hispanics and blacks.  
8       What I think the sponsor has done adequately is  
9       ensure that patients that did come from the U.S.  
10      actually corresponded to the U.S. population.

11           DR. SMITH: Further comments? Dr. Fojo?

12           DR. FOJO: Just one quick comment. Like  
13      you, I'm concerned about censoring always when I  
14      see it. But it's a little bit reassuring here,  
15      that if you look at the censoring rate, it actually  
16      appears comparable. The overall number was  
17      comparable, and the rate appears comparable. So  
18      it's not like you're censoring one faster than the  
19      other.

20           DR. PACKER: It doesn't really pertain here,  
21      but comparability of censoring is not assurance of  
22      balance. It just isn't. And we don't know why

1       they stopped. It could be for different reasons.

2               DR. FOJO: Oh, sure.

3               DR. PACKER: Or it could be because of  
4       progression of disease.

5               DR. FOJO: Right. The drug could be  
6       eliminating the bad ones --

7               DR. PACKER: Right.

8               DR. FOJO: -- and the good ones could be  
9       leaving the placebo. Since we don't have any other  
10      information, I think it's good to look at that sort  
11      of thing.

12              DR. PACKER: I just wanted to make the  
13      point. I don't actually want to suggest that  
14      there's a problem here. It's just the data are  
15      sparse. It's censored. The fact that they're  
16      comparable is nice, but it doesn't really help that  
17      much.

18              DR. SMITH: Dr. Lewis?

19              DR. LEWIS: I just have a comment. I think  
20      they jumped through the hoop that they were asked  
21      to, and that is the current guideline. However, it  
22      disturbs me that out of 5700 people on dapa,



1       230-some even have two or three years follow-up,  
2       three years I guess; 170 have four years follow-up.  
3       And yet there were so many studied for a short  
4       time.

5               I think it may bear -- a lot of the issues  
6       we're talking about might have been better  
7       clarified if there were a larger number of patients  
8       followed for a longer time. And perhaps rather  
9       than doing short studies, comparing it to every  
10      other diabetic drug in the universe, each for 20  
11      weeks or something, we should encourage some longer  
12      studies to try and get long-term risk and long-term  
13      experience.

14             DR. SMITH: So I -- yes, Dr. McBryde?

15             DR. MCBRYDE: Kevin McBryde. The  
16      cardiovascular data to me is interesting. I was  
17      looking at -- it didn't seem to get a lot of  
18      attention, but FDA slide 27 --

19             DR. SMITH: Dr. Packer, if you would turn  
20      your mic off, I think we can get that interference  
21      out.

22             DR. PACKER: Sorry about that.

1 DR. MCBRYDE: But FDA slide 27, looking at  
2 the demographics and the baseline characteristics  
3 of studies 18 and 19, you're looking at a  
4 population where there's 96 percent hypertension  
5 versus 60 percent. In all the other studies,  
6 99.5 percent have a history of cardiovascular  
7 disease versus 18 percent. Eighty-five percent are  
8 dyslipidemic versus 50 percent of the control  
9 groups. Hypertension is far more common in that  
10 group.

11 At least looking at the math, what I see is  
12 out of 135 MACE events, 87 of them were in the  
13 roughly 1800 in these two groups that were very  
14 enriched for what I think of as the high risk  
15 diabetic population. That leaves 40-plus events  
16 across the other 7,000 patients studied. I'm not  
17 really reassured by the Kaplan-Meier curves mainly  
18 because by 12 months, over 50 percent of the  
19 patients disappeared. And so after that first year  
20 of data, I think it's being driven by very small  
21 sample sizes and very few events, as has been  
22 discussed.

1           When I think about 18 and 19, the overall  
2       hazard ratio was 1.11, but the 95th percentile  
3       upper confidence limit broke 1.8. So I do feel  
4       some concern in that population. When I looked at  
5       the blood pressure data, my first thought was the  
6       differences between the dapagliflozin-treated group  
7       and the placebo was 3 to 4 millimeters of mercury.  
8       The standard of error for good auscultatory  
9       measurement of blood pressure is plus or minus  
10      2 millimeters of mercury. And in fact, looking at  
11      the mean blood pressure and the mean decrease in  
12      blood pressure, essentially using JNC 7 guidelines,  
13      you're going from stage 1 hypertension to stage 1  
14      hypertension.

15           I don't think it's buying you really  
16      anything, and I doubt that that benefit -- even if  
17      it may be statistically significant, I don't think  
18      it's clinically meaningful, and I don't think it's  
19      really going to speak to reducing the  
20      cardiovascular risk in a population, particularly  
21      in 18 and 19, that look very, very high risk for  
22      adverse cardiovascular events, the MACE events.

1           With regard to the hypertension, the other  
2       thing that struck me is in the pediatric  
3       population -- and I'm a pediatric  
4       nephrologist -- with known SGLT-2 transport defects,  
5       what have we seen? There are small studies that  
6       demonstrate that they do develop a natriuresis from  
7       blockage of the sodium-glucose co-transporter.  
8       They also develop hyperammonemic, hyperaldo states,  
9       consistent with the renin angiotensin aldosterone  
10      system.

11           All of the patients in the two trials  
12      looking at hypertension were all treated with ace  
13      inhibitors and ARBs. I'm not surprised that they  
14      found some benefit, but I doubt it's the  
15      dapagliflozin. And it just happened to be that  
16      probably use of Ras inhibition was the appropriate  
17      hypertension therapy for this particular  
18      population, in the pediatric population at least,  
19      where we know that they've got activation of the  
20      Ras pathways.

21           DR. SMITH: So I'm going to try to  
22      summarize, but before I do that, from the FDA

1 perspective, are there some points here that you  
2 haven't heard addressed that you'd like comment on  
3 with regard to this question?

4 DR. GUETTIER: The last bullet was trying to  
5 get to any residual uncertainties that you want  
6 worked out. And specifically, is anyone concerned  
7 about the imbalance in early events that was  
8 identified in this program and another program with  
9 a similar mechanism of action?

10 DR. SMITH: Anyone want to comment on that?  
11 Yes, Dr. Savage?

12 DR. SAVAGE: Yes. I think that that also is  
13 something that should be kept in mind if the drug  
14 is approved and goes forward, and there's a  
15 follow-up study to go along with it because those  
16 numbers are small. They could be spurious, but  
17 they could also be -- since they occurred in the  
18 other sister drug also, there's something we just  
19 don't have enough data on, and it should be an area  
20 of attention.

21 DR. SMITH: Dr. Vos?

22 DR. VOS: Miriam Vos. And I was basically

1       going to say the same thing. I think it's  
2       something that needs to be paid attention to. But  
3       I think looking at the data imbalances that occur  
4       over each of the subsequent months, which seem to  
5       go back and forth and back and forth between the  
6       control and the treated groups, I think you can't  
7       really make anything of it statistically. But it's  
8       a good thing to follow forward.

9               I was also reassured by the fact that when  
10       they looked at the cases, it didn't seem to be a  
11       hypovolemic-induced episode. So it didn't  
12       mechanistically fit with what the drug would be  
13       doing.

14              Then I will weigh in on kind of a bigger  
15       discussion on A and B super briefly. I feel that I  
16       was reassured by the fact that both the FDA and the  
17       sponsor had the same conclusion on the  
18       cardiovascular risk and sum. And so I think that  
19       that's an important area to pay attention to as we  
20       think about this because there really wasn't a  
21       disagreement between the analyses of the data. So  
22       I was reassured by that.

1           Then finally, I was also reassured by the  
2       large number of patients in study 18 and 19. Those  
3       are very high risk. I think the whole population  
4       is high risk, but 18 and 19 is very high risk, and  
5       there wasn't a strong signal. So there should have  
6       been a strong signal if there's a large increase or  
7       a significant increase in risk from the drug.

8           DR. GUETTIER: If I can clarify just one  
9       point, I think the question that was asked was  
10      whether or not we agreed with the prespecified  
11      analyses results, and that we do agree with. Now,  
12      as you heard today, we also looked at other  
13      analyses that were not prespecified, and those were  
14      the larger meta-analysis, and then the subgroup by  
15      18 and 19. And there we had very divergent points  
16      of view within the agency as to what each of those  
17      studies meant. And that's why we wanted you to  
18      weigh in on it.

19           DR. SMITH: Dr. Wilson?

20           DR. W. WILSON: So I just wanted to ask the  
21      following question. I know there's been some  
22      concern about the censoring and whether or not this

1       lost data might be hiding a signal. I think that  
2       in fact the cardiovascular risk, if there is any,  
3       you can either have it due to the drug being on  
4       board, or you can have more of a long-term  
5       physiological effect, and therefore, it's going to  
6       last.

7               Clearly, if it is the former, then by  
8       getting more data points after someone comes off  
9       the drug, you're actually going to be moving more  
10      toward a null, and therefore diluting out any  
11      effect. However, if it is a long-lasting effect,  
12      then censoring will happen.

13             So my question is, either to the sponsor or  
14      to the FDA -- because this is not my field or other  
15      members of the committee -- for those diabetic  
16      drugs that have shown increased cardiac side  
17      effects, are these effects primarily during the  
18      time that the drug is on board or are they effects  
19      that last; and therefore, when the drug comes off,  
20      you still have a relatively high rate of increased  
21      cardiac effect, adverse effect. And if so, how  
22      long does that generally last?



1 DR. PACKER: Just one question I have as a  
2 clarification, does the FDA currently recognize any  
3 anti-diabetic drug as being associated with an  
4 increase in cardiovascular risk?

5 DR. ROSEBRAUGH: Sulfonylureas are labeled  
6 as a group that's on a --

7 DR. PACKER: But that's 30 years old, right?

8 DR. ROSEBRAUGH: Yes, it's very older data.  
9 I think you probably have all followed some of the  
10 rosiglitazone stuff. We are continuing to evaluate  
11 that.

12 DR. PACKER: So I just wanted to -- you said  
13 that other drugs that increased cardiovascular  
14 risk, and I just didn't know of any.

15 DR. SMITH: Well, now you know. So could  
16 the FDA or the sponsor answer the question. Thank  
17 you.

18 DR. ROSEBRAUGH: Let me try to get a little  
19 bit to that. And the statisticians can chime in,  
20 too. On the outcome studies, when we do  
21 evaluations, we do an ITT and a per protocol. And  
22 we do specifications. Like we'll see 30 days after

1 the drug, 60, 90, and some of that's because,  
2 you're right, you don't know.

3 Is there some kind of a long-term effect  
4 that could happen that causes plaque instability  
5 that happens down the road or what. So we kind of  
6 do multiple analysis. That may prespecify one, but  
7 we say we're going to look at both with interest.  
8 And so we try to get to some of those issues  
9 because we don't know either.

10 DR. W. WILSON: So then I guess we don't  
11 know, but is there any -- well, it's going to be  
12 drug by drug. I mean, from what I can see about  
13 the mechanism of this drug, it would seem that it's  
14 more likely that the adverse effects, if they're  
15 present, would be effects that would be occurring  
16 while the drug is on board. It's hard to believe  
17 that small perturbations in LDL, et cetera, which  
18 usually accrue adversely over years and years,  
19 would really be durable in the exposure time for  
20 this.

21 I'm only bringing this up because there's  
22 been a lot of discussion over censoring and what

1       happened. And it seems to me that the totality of  
2       the evidence would point toward there likely not  
3       being something hidden, but of course one can never  
4       know.

5               DR. SMITH: Dr. Lewis?

6               DR. LEWIS: I just want to comment that I  
7       think the early 30-day cardiovascular event thing,  
8       I mean, you could hypothesize that it is a  
9       potential reality. In that, I think volume  
10      depletion is poorly assessed by any measure. I  
11      mean, MedDRA, I would totally not assume they  
12      didn't miss any volume depletion.

13              However, in fairness, I would say that I bet  
14      you it's true. For any kind of diuretic you put a  
15      patient on, there's probably a very small subset of  
16      them who's pressure just drops a little bit low or  
17      whatever, and it overshoots what they can tolerate.  
18      So it actually doesn't disturb me that it couldn't  
19      conceivably be true. And I think if we studied  
20      Lasix, we'd probably find the same thing.

21              DR. PACKER: I know of no evidence anywhere  
22      that diuretics provoke an increase in

1       cardiovascular events at any time during treatment.  
2       Just for the record. I don't know of any evidence  
3       that they do.

4               DR. LEWIS: So I agree with you that in the  
5       totality, they don't. But I'm not sure -- you  
6       know, Lasix was approved many, many, many years  
7       ago. I don't know. We'd all have to go back to  
8       look to see if there was a small early 30-day  
9       signal. I mean, we're talking about the early  
10      30-day, not the totality at the end of the day.

11             DR. PACKER: We have a lot of data on Lasix.  
12      We have a lot of data on thiazide diuretics. We  
13      have no data that volume depletion provokes  
14      cardiovascular events of this type.

15             DR. SMITH: So I would like to summarize,  
16      and there will be opportunity to add if I've left  
17      something out, or if you have thoughts that I don't  
18      include.

19             Dr. Hiatt, I'm particularly look for any  
20      input from you because you were breaking up a bit  
21      on the microphone there when you were making your  
22      comments.

1 DR. HIATT: Okay.

2 DR. SMITH: So anyway, the comments from  
3 several members of the group noted that there was  
4 not particular concern about a convincing signal  
5 for increased cardiovascular events. It was noted  
6 that the overall population in the pool-up studies  
7 was likely the most informative.

8 In regard to that, it was also noted that  
9 the conclusions don't really fundamentally change  
10 as the different subgroupings of studies -- that is  
11 study 18/19 -- versus the overall studies are  
12 considered. And there were actually variable  
13 opinions expressed where one or more members felt  
14 there was not a safety signal for cardiovascular  
15 disease, whereas at least one other member  
16 expressed concern that there might be a possible  
17 cardiovascular risk signal.

18 In evaluating the data, the view was  
19 expressed that fundamentally there are not enough  
20 cardiovascular events to really allow a confident  
21 evaluation of the risk. And it was noted that the  
22 planned longer-term trial in fact would be needed

1 and would be likely to resolve that concern.

2 In regard to further trials or future  
3 trials, one comment from the committee members was  
4 that data from short-term trials, even if they're  
5 multiple data with lots of subjects, are ultimately  
6 perhaps less informative than longer-term trials,  
7 and that consideration should be given to the value  
8 of longer-term trials.

9 In regard to the studies that have been  
10 completed, there was concern about the potential  
11 role of censoring. The statement was made that the  
12 sensitivity data are helpful, somewhat reassuring.  
13 Again, in regard to the studies that have been  
14 completed, there was concern expressed about the  
15 lack of diversity in the study's sample, and a  
16 comment was made that this may, in part, reflect  
17 the populations that participated in those studies  
18 with lower representation of certain population  
19 groups than perhaps what characterizes the U.S.

20 Moving to comments about some of the other  
21 observed changes such as blood pressure, weight,  
22 glycemic control, and lipid parameters, there were

1 viewpoints expressed that several of these,  
2 specifically blood pressure and lipid parameters,  
3 were modest in change and likely to be small in  
4 their overall impact.

5 The comment was made that even though the  
6 weight change is modest, that even a modest change  
7 in the direction of weight loss can have  
8 substantial impact in terms of actual use of a drug  
9 in clinical practice, improving patient adherence.

10 There was some specific comment about the  
11 question of early events being increased with dapa,  
12 and the comment was made from the panel that this  
13 was not an issue of great concern. There's a  
14 possibility that those early events certainly could  
15 be spurious. But because of the small numbers,  
16 it's very difficult to have a clear understanding  
17 of that, and that that certainly should be  
18 evaluated in future studies.

19 In regard to additional concerns, there was  
20 also comments made about potential differences in  
21 pediatric populations, particularly in regard to  
22 potential effects of this drug on fluids and

1 electrolytes, and that should be considered in  
2 terms of perhaps ultimate populations for use of  
3 the drug.

4 A comment was also made as a acknowledgment  
5 that the data from the studies was carefully  
6 collected, in general, in a well-designed way, and  
7 with the acknowledgment that the guidelines for  
8 cardiovascular studies from the FDA are something  
9 that have been evolving over time and somewhat  
10 after the start of a number of these studies as  
11 well.

12 So I'll end my summary there, and please  
13 help me out here with any additions or corrections  
14 that anyone would like to make.

15 Dr. McBryde?

16 DR. MCBRYDE: I apologize. I wasn't trying  
17 to speak to a pediatric indication for  
18 dapagliflozin. I was merely trying to say that in  
19 that pediatric population with inherited proximal  
20 tibiofibular dysfunction of the sodium-glucose-2  
21 co-transporter, that it is known that they develop  
22 hyperammonemia and activation of the renin



1     angiotensin aldosterone system, that may play a  
2     role in what we see from the cardiovascular  
3     effects, as well as the blood pressure effects with  
4     dapa; that those may be completely independent of  
5     the benefit of dapagliflozin, that in fact it may  
6     be that -- because in the hypertension studies,  
7     they were all treated with ACE and ARB, that that  
8     may have been the most effective therapy to be  
9     using for that population. But not asking for a  
10    pediatric indication. I don't think they're asking  
11    for a pediatric indication.

12           DR. SMITH: So would you transition that  
13    into a comment specifically directed to this  
14    question?

15           (No response.)

16           DR. SMITH: That's just a comment of caution  
17    and further thought?

18           DR. MCBRYDE: Yes. I think so. I don't  
19    think there's a direct --

20           DR. SMITH: Dr. Wilson?

21           DR. P. WILSON: Peter Wilson. Perhaps to  
22    reinforce, it might give approbation to ACE and ARB

1 inhibition treatment for the Ras system for such  
2 patients, but we're already supposed to be doing  
3 that for our diabetic patients anyway.

4 DR. SMITH: Any other comments on this  
5 question?

6 (No response.)

7 DR. SMITH: Okay. Then I think we'll move  
8 to question number 2.

9 We actually have reached a point of where  
10 we're supposed to take a break. So we'll take a  
11 short, 10-minute break, and then we'll resume. So  
12 back here in 10 minutes, please.

13 (Whereupon, a recess was taken.)

14 DR. SMITH: We're going to restart the  
15 session now, if you would all please take a seat  
16 promptly. We're going to start with a brief  
17 correction to the record from Karen Abraham-  
18 Burrell.

19 DR. ABRAHAM-BURRELL: Thank you. I need to  
20 state a correction into the record. This morning  
21 in the meeting statement, I read that conflict of  
22 interest waivers have been issued in connection

1 with this meeting, and this is in error.

2 For the record, there were no waivers issued  
3 in connection with this meeting. Thank you.

4 DR. SMITH: Thank you.

5 We will now proceed to discussion question  
6 number 2. Can I have that posted, please? I'll  
7 read the question. Again, this is for discussion.

8 Based on the information provided in the  
9 briefing package and the presentations at today's  
10 meeting, discuss your level of concern with regard  
11 to the observed association between dapagliflozin  
12 use and occurrence of cancer identified in the  
13 application. Specifically comment on whether you  
14 believe use of dapa is associated with an increased  
15 risk of bladder cancer and explain your rationale.

16 Dr. Wyndham Wilson.

17 DR. W. WILSON: I guess the reason why  
18 myself and Dr. Fojo are here are mostly for the  
19 cancer risk. That clearly doesn't keep me from  
20 opening my mouth on things I don't know anything  
21 about. Anyway, let me talk about cancer.

22 We know that the overall hazard ratio for

1 all tumor types was essentially 1. And when we  
2 look at the sensitivity analyses, we can see that  
3 there's everything from a trend, but  
4 nonstatistically significant increase, in bladder  
5 cancer to actually a very hopeful decrease in blood  
6 and lymphoid cancer. So I'm thinking about maybe  
7 using this to try to prevent cancers in lymphoid  
8 diseases. That's meant to be humorous.

9 So let's just focus on the bladder cancer,  
10 and there were 10 cases. I myself am somebody that  
11 am very sensitive to a drug that could cause  
12 cancer, and I think there are a number of more  
13 reassuring aspects when one really drills down to  
14 the actual cases themselves.

15 First, I think it is important for me that  
16 6 out of 10 occurred within a 6-month time frame.  
17 And we all know that tumorigenesis is a process  
18 that evolves over usually years. One can, with  
19 highly carcinogenic agents, possibly induce them  
20 quicker, but they usually occur over years. And  
21 here we have 60 percent of all the tumors occurring  
22 within six months.

1           It is also a little bit reassuring that in  
2   most of the cases, there was preexisting hematuria,  
3   which is a marker for an increased risk of having  
4   bladder cancer. Now, that has to be taken with a  
5   grain of salt because it's also commonly seen in  
6   diabetes overall, and so one has to be careful  
7   there.

8           Then I guess the final thing that reassures  
9   me to some extent is looking at the distribution of  
10   the types of cancers that are seen in terms of the  
11   degree of invasiveness.

12           Now, here we're talking about very small  
13   numbers. But at least as presented, and I'm not an  
14   expert in genitourinary cancers, but that  
15   75 percent in a large population are usually  
16   considered to be noninvasive or non-muscle-invasive  
17   tumors. I think that it's reassuring that 8 out of  
18   10 in this case were similarly noninvasive.

19           Now, these are getting down to very small  
20   numbers. If in fact this drug was cancer-causing  
21   or cancer-promoting, I might expect, especially  
22   early on, that I would see more superficial tumors

1 if this could in fact induce that within a few  
2 months.

3 But more importantly is that for the later  
4 cancers, I might expect that if it was an inducer,  
5 I would see a higher rate of invasive cancers. And  
6 relative to the underlying rate of invasive  
7 cancers, that doesn't seem to be any different than  
8 what a normal population would have.

9 So I look at this data, not telling me that  
10 I absolutely don't have a risk here, and of course  
11 this is also in the context of all of the in vitro  
12 models that people have done, not showing that the  
13 drug itself is carcinogenic. But I do realize that  
14 the microenvironment isn't tested in those models.

15 But I don't have enough concern about this  
16 that I would consider this to be a safety signal  
17 that, at least for me as an oncologist, would keep  
18 me from wanting to approve it. However, I would,  
19 in the postmarketing setting, be very cautious  
20 about looking for this, monitoring for it. And  
21 it's my understanding those kinds of studies are  
22 already ongoing.

1 DR. SMITH: Dr. Thomas?

2 DR. THOMAS: Thank you. I think there's a  
3 couple things I just wanted to mention. One is the  
4 weight of hematuria in the overall study, this  
5 15 percent. That's consistent with what you would  
6 see with people with diabetes, who have some  
7 element of microalbuminuria. That's what's been  
8 estimated in one study looking at this, 8 percent  
9 with all people with microalbuminuria, increasing  
10 as high as 35 percent with macroalbuminuria.

11 But unfortunately, that's not reassuring in  
12 terms of detection because then you can't use  
13 hematuria as a real good guide to decide who's at  
14 greatest risk because as people's kidney disease  
15 worsens, that will happen.

16 But of course, if they really do have severe  
17 kidney disease -- and they don't have to have that  
18 severe; stage 3 -- they wouldn't be on this drug,  
19 so that might be positive in terms of the labeling  
20 indication.

21 What does bother me is if it's not related  
22 to the drug because of the time frame, if you have

1       sufficient enough subjects for randomization, the  
2       power of the number of subjects should actually  
3       randomize hematuria and diagnosis to both groups  
4       evenly. And you see a disparate assortment. So  
5       that's kind of puzzling.

6               When you have thousands of individuals in  
7       each arm, you would expect randomization would  
8       hopefully account for that, if it's just a  
9       detection at the start of the study or within a few  
10      months.

11             Biologically it doesn't make a lot of sense  
12      right now. But there may be things that will be  
13      discovered, so I think that postmarketing studies  
14      will be very important.

15             The basic science studies will be important  
16      as well, and the interplay with this agent on  
17      kidney function in terms of albumin excretion or  
18      concentration of toxins that might be increased in  
19      the urine because of increased urinary flow rates  
20      and retention.

21             The one thing I am concerned about is  
22      actually breast cancer, and the reason I'm



1       concerned about this is bladder cancer is something  
2       that you could pick up as a signal because it's not  
3       as common. But breast cancer is common.

4               So if you use the old story they used in  
5       high school English -- dog bites man, it's not  
6       news; man bites dog, it is -- if a woman develops  
7       breast cancer, no one's going to necessarily  
8       identify that as an event related to the drug.

9               So there has to be robust surveillance,  
10       probably from databases, to establish if there's an  
11       ongoing risk with breast cancer. Even if it's not  
12       biologically related, I think just simple reporting  
13       of cases won't happen because people just assume  
14       that breast cancer is from normal risks because of  
15       aging.

16               So I think you have to have some other type  
17       of process, similar to maybe what was done with  
18       pioglitazone and bladder cancer, where they went  
19       through the Kaiser databases to look and identify  
20       cases. So I think that will be important for  
21       breast cancer.

22               DR. SMITH: I'm sorry. I wasn't able for

1       some reason to hear very clearly in the very final  
2       part. So could you state clearly what your  
3       recommendation is again?

4               DR. THOMAS: I think you have to have some  
5       type of follow-up or surveillance that's beyond  
6       just case reporting from practitioners because  
7       breast cancer is so common, utilizing some type of  
8       database, such as was done with pioglitazone and  
9       bladder cancer. They used the Kaiser Permanente  
10      database to look at risk.

11             Things like that -- population-based  
12      databases to look at risk would probably be a way  
13      of making sure you're not missing cases just  
14      because breast cancer is very common.

15             DR. LIST: Mr. Chair?

16             DR. SMITH: Yes?

17             DR. LIST: I just want to clarify very  
18      quickly. We, in our pharmacoepidemiology studies  
19      and in our DECLARE study, we're also looking at  
20      breast cancer. We're adjudicating it in DECLARE.  
21      And we have, similar to what you're suggesting,  
22      large database pharmacoepidemiology studies

1       ongoing.

2               DR. SMITH:   Thank you.

3               Dr. Brittain?

4               DR. BRITTAIN:  I certainly don't have much  
5       to add to these very excellent discussions.  I  
6       can't escape the possibility that there is a risk.  
7       I think it's a reasonable probability that it's  
8       just a chance finding, but it's still there.  I'm  
9       still uncomfortable with it.

10              I do kind of wonder -- when you look at the  
11      subgroup of people who have hematuria -- am I  
12      saying that right -- at baseline, I think it was 6  
13      to 1.  I know the groups are 2 to 1, so that  
14      doesn't sound so bad.  But I think that's the right  
15      way to think about it, is not just to look back at  
16      the cases and say they had hematuria, but to look  
17      at the subgroup with hematuria and understand that  
18      risk difference.

19              But overall, I guess I have to say, based on  
20      what I'm hearing from everybody else, that it  
21      doesn't seem that biologically plausible.  But I  
22      guess I still wonder, if you're in a precancerous

1 state, if there's something that just tips you  
2 over. And that thought is still in my mind as a  
3 possibility.

4 DR. SMITH: Dr. Fojo.

5 DR. FOJO: I think none of us are ready to  
6 dismiss it, which is what you're alluding to. I  
7 think even the sponsor obviously is doing a lot.  
8 But I thought that just because we don't have an  
9 explanation for it doesn't mean that one doesn't  
10 exist. So consequently, you can't dismiss it. You  
11 just need to be careful.

12 I thought Dr. Ning, who did the consult for  
13 the FDA, and it's cited here, is right on the  
14 money. It's excellent. It should be further  
15 studied and carefully monitored. And I think that  
16 is what is planned, and that to me is quite  
17 reassuring.

18 DR. SMITH: Any other comments on this  
19 discussion question? Yes, Dr. Lewis?

20 DR. LEWIS: Well, when I reviewed these  
21 materials this was the thing that troubled me the  
22 most. Actually, nothing else did. And I guess

1 just to be a little bit of a devil's advocate, and  
2 I would really welcome Dr. Wilson's and Dr. Fojo's  
3 comments on this, is there is another drug in this  
4 class that's out there. So this isn't like a  
5 totally unmet need.

6 People who are participating in the DECLARE  
7 study have assumed voluntarily a risk. But if we  
8 approve this, we will be imposing that risk on a  
9 worldwide, or at least a U.S. population, I guess.

10 How smart should we be about this probably  
11 isn't really a signal of 14 to 5, if you combine  
12 the cana and the dapa groups. I wonder if you  
13 could just comment on that because I actually was  
14 so happy to see you guys on the panel.

15 DR. SMITH: Dr. Wilson.

16 DR. W. WILSON: Thank you. I just want to  
17 echo what everyone says, that I don't think that we  
18 can dismiss this. But they look at a lot of  
19 different cancers. And if you look at a  
20 sensitivity analysis, it goes from reducing them to  
21 increasing them. And the thing with bladder cancer  
22 is that if you don't look, you don't find, because

1       they're often asymptomatic.

2               So I think the fact that most of these were  
3       found within six months, it's hard to imagine that  
4       the drug did that. There's not more invasiveness,  
5       which is what you would expect a tumor promoter  
6       would do. And I think human nature, when you're on  
7       an experimental drug, to be a little more cautious.  
8       And so I'm very suspicious because these were  
9       not -- if I'm correct, these were not blinded  
10      trials. Right? These were not blinded trials.  
11      Correct?

12             DR. PACKER: They were blinded.

13             DR. W. WILSON: They were blinded? All of  
14      these trials were blinded?

15             DR. LIST: Yes. That's correct. These were  
16      all blinded.

17             DR. W. WILSON: All right. Well, then I  
18      can't say that people looked more vigorously in the  
19      treatment arm. But I'm very suspicious that this  
20      all could be generated, or I think it's likely it's  
21      just generated by imbalance of looking. That's  
22      what I think because a real in-depth look at this

1 data doesn't really add up for me that it's likely.  
2 But at the same time, I think it needs to be  
3 watched.

4 I think it's up to the FDA as to whether or  
5 not they think it rises to that level vis-a-vis the  
6 fact that there's another class of this agent on  
7 the market. But I'm looking at this independent of  
8 that. At least from my point of view, I'm not  
9 looking at this vis-à-vis there is another class  
10 out there; therefore, this is going to be more  
11 worrisome to me. I'm looking at them  
12 independently.

13 DR. SMITH: Comment from the FDA?

14 DR. NING: Thank you. I'd like to reiterate  
15 that the risk factors, including baseline  
16 hematuria, were well-balanced between the dapa and  
17 the control arms in 21 trials, that included about  
18 10,000 patients.

19 So I think the key issue here is how to  
20 assess the clinical relevance of the increase of  
21 bladder cancer diagnosis in association with use of  
22 dapagliflozin. I think it is harder to assess

1 causality relationship for this short term of  
2 treatment, median treatment only about one year.

3 DR. SMITH: Yes, Dr. Packer?

4 DR. PACKER: I think when you have a split  
5 of 9 to 1, you have 10 events, you don't know. We  
6 don't know. There's no way of knowing. Biological  
7 rationale, clinical judgment, is not terribly  
8 reliable here. The fact that there's decreases in  
9 certain cancers and increases in others doesn't  
10 mean that there isn't an increase in this cancer.

11 I keep on looking at the pioglitazone  
12 example, which showed an imbalance with small  
13 numbers of events, and all sorts of rationales were  
14 provided. It was only years later, largely not  
15 from randomized trials but from observational  
16 studies, that there was a consistent relationship  
17 with bladder cancer.

18 So I don't think that we can dismiss it. I  
19 don't think we can know. And I would just rely on  
20 the FDA to mention it in the label so that people  
21 are aware of the possibility and that observational  
22 studies in the future can identify whether it's



1 real or not.

2 DR. SMITH: Other comments? Yes,  
3 Dr. Wilson?

4 DR. W. WILSON: Let me just comment that at  
5 least I hope that I'm not giving any impression  
6 that I think it should be dismissed. I fully agree  
7 with the postmarketing plan. But with regard to  
8 the example that was given, I don't know the  
9 specifics of why cases were felt not to be related  
10 to cancer. But it's not clinical judgment, it's  
11 first principles of tumorigenesis that I'm applying  
12 here.

13 It's also possible that with that other  
14 example, that it's true true, but unrelated. That  
15 is, it may be that they did find a signal, but in  
16 fact, maybe that signal, if it was a very early  
17 signal, wasn't related to the drug but, in fact,  
18 over time, the tumorigenic properties of the drug  
19 did begin to show up in longer-term use.

20 So that example again without the specifics  
21 can't be used to say, hey, they missed it because  
22 they may not have missed it. It may have been a

1       spurious finding. So it was true true but  
2       unrelated. And I just want to put that out.

3               DR. SMITH: So shall I try to summarize?  
4       What the advisory committee opinion is in regard to  
5       this question is that, first of all, it was noted  
6       that it's reassuring that overall cancer  
7       risk -- that is, risk for all cancer  
8       types -- essentially had a relative risk of 1.

9               It was noted that there is some variation in  
10       individual cancers. The one that has been given  
11       particular attention is bladder cancer, for which  
12       there were 10 cases within the various dapa study  
13       populations.

14              Various members of the group have expressed  
15       the opinion that they consider, based on a review  
16       of all the data, that bladder cancer represents a  
17       potential risk but not a convincing risk in  
18       patients treated with dapa. And this in part  
19       reflects the fact that there really were a small  
20       number of events available for evaluation as well  
21       as consideration of other aspects of the data.

22              In terms of the specifics of those bladder

1 cancer cases, it was noticed that there are a  
2 number of reassuring aspects based on individual  
3 case reviews. This included noting that 6 of the  
4 10 cases occurred within the first 6 months, and  
5 this is a much shorter time than would be  
6 anticipated if tumorigenesis were occurring in  
7 response to the drug.

8 It was also noted that 8 of the 10 were  
9 noninvasive cancers. And if the drug had  
10 substantial effects as a tumor promoter, it was  
11 anticipated that one would see more advanced or  
12 more invasive cancers. So those were considered  
13 reassuring aspects.

14 There was a general consensus that the data  
15 do not raise a level of concern that would lead to  
16 wanting to see further study on the bladder cancer  
17 risk prior to approval if the drug ultimately is  
18 approved, but that this definitely should be  
19 addressed in post-approval or postmarketing  
20 studies.

21 One note was made by one of the members of  
22 the advisory committee, that the FDA should take

1       into consideration that there is another drug in  
2       the same class. And so in evaluating bladder  
3       cancer risk for dapa, it should be recognized that  
4       there is an alternative drug available to patients.

5               Concern was expressed by one member of the  
6       committee about breast cancer. And that individual  
7       felt that it would be important to include an  
8       evaluation of breast cancer in postmarketing  
9       studies if the drug is approved that should involve  
10      more than just case reporting, but some sort of  
11      database evaluation that might be a better way of  
12      identifying whether or not there is an association  
13      between use of the drug and breast cancer risk.

14             Any members of the committee would like to  
15      make corrections or additions to that summary?

16             (No response.)

17             DR. SMITH: Okay. We'll move to the next  
18      discussion question, question 3. This is on liver  
19      toxicity.

20             Based on the information provided in the  
21      briefing package and the presentations at today's  
22      meeting, discuss your level of concern with regard

1 to dapagliflozin use and drug-induced liver injury.  
2 Specifically comment on whether you believe use of  
3 dapagliflozin is associated with an increased risk of drug-  
4 induced liver injury and explain your rationale.

5 So this is open for discussion or comment.  
6 Yes, Dr. Vos?

7 DR. VOS: I feel the same way. Now I can  
8 finally talk about something I know as a  
9 hepatologist.

10 I think that it's important to consider the  
11 background of diabetes medications. Several of the  
12 important drugs that are used now have known  
13 hepatotoxicity. And so to have a drug that has  
14 less hepatotoxicity would be beneficial. Also,  
15 diabetes patients are a population that's enriched  
16 for liver disease because of the increased  
17 prevalence of NAFLD amongst that population.

18 So if we give a drug to a population that's  
19 enriched for underlying liver disease, you would  
20 likely see a strong signal if that drug was  
21 hepatotoxic. So I would have expected to see the  
22 ALT go up. And the data was reassuring because

1       there was really no difference between control and  
2       the drug.

3               So from that standpoint, I didn't see  
4       convincing evidence that there was any liver  
5       effects of this medication. The one case of DILI,  
6       I think, similar to rare events that we've  
7       discussed, like the bladder cancer, I think it's  
8       very difficult.

9               When you do treat, many patients, if there  
10      are people that have a polymorphism that makes them  
11      more susceptible to a severe liver injury from a  
12      medication, those couple cases will show up when  
13      you enroll more thousands and thousands of  
14      patients.

15              So I think it's something that will need to  
16      be observed. But I don't think it's unexpected to  
17      have one case of fairly severe liver disease  
18      amongst an older population of this size.

19              DR. SMITH: Any other comments?

20              (No response.)

21              DR. SMITH: I'll just comment that I  
22      completely agree, that I find the follow-up review

1 of the one patient with the severe liver response  
2 to be reassuring that it was most probably not  
3 drug-related, although of course in a single case  
4 one cannot conclusively exclude that.

5 But I really saw very little compelling  
6 reason to be alarmed that that was a signal case of  
7 liver toxicity from the drug. And I felt that the  
8 pool of data otherwise really did not provide a  
9 signal for liver disease. And I think your  
10 comments are very helpful in regard to the  
11 background that one is observing this in, in terms  
12 of risk in diabetes patients.

13 Other comments on that?

14 (No response.)

15 DR. SMITH: I'll try to summarize this,  
16 which is that the advisory committee did not have  
17 substantial concern about liver disease occurring  
18 in patients on dapa; that the data overall, the  
19 summary of the data, do not appear to provide a  
20 significant signal for risk of liver disease; that  
21 the one patient who had an acute hepatitis  
22 response, based on the data of that patient

1 followed over time after discontinuation of the  
2 drug with some recurrent events in terms of flares  
3 of the liver disease, provided some substantial  
4 reassurance that that was not drug-related,  
5 although that cannot be absolutely conclusive.

6 It was noted that this lack of evidence for  
7 concern about liver disease is occurring in a  
8 disease background in diabetes, and perhaps  
9 diabetes with other drugs, both of which are  
10 associated with some increased risk of liver  
11 disease. So it's even more reassuring that a risk  
12 signal is not evident.

13 Nevertheless, given those risks in a  
14 diabetes population, it was considered important to  
15 monitor for liver disease, or the FDA should at  
16 least consider monitoring for liver disease  
17 postmarketing if this drug is approved.

18 Any additions? Corrections? Deletions?

19 DR. PACKER: As I understand it, for these  
20 cases of drug-induced liver injury, I thought that  
21 monitoring for a liver function test was not very  
22 useful because they occur precipitously without a



1 warning signal. Am I right or wrong here?

2 DR. PUCINO: Yes. Frank Pucino. Our  
3 hepatology consultant, Dr. Senior, suggested that  
4 the label should appropriately warn in the Warnings  
5 and Precautions that this could be a potential  
6 issue, and that patients should be warned to report  
7 signs and symptoms to their clinicians.

8 DR. PACKER: As opposed to monitoring?

9 DR. PUCINO: As opposed to routine  
10 monitoring. Correct.

11 DR. VOS: I can just clarify. It's two  
12 different types of injury. So the Hy's law  
13 increase in bilirubin and doubling/tripling in the  
14 ALT, that combination is a signal of a severe liver  
15 injury that fits in the category of DILI. But then  
16 medications can also have more mild liver injury  
17 that then could be cumulative. And so you would  
18 see that in rises in ALT.

19 But you're correct, the sudden change in  
20 bilirubin and rise in liver enzymes would be a  
21 different scenario that's usually rare, even in the  
22 drugs that we know cause it.

1 DR. PACKER: Yes. I only say that because I  
2 always think there is some entertainment value to  
3 the FDA saying that people should monitor liver  
4 function tests because I'm not certain that they're  
5 picking up the right thing. And two is, I'm almost  
6 certain that physicians don't listen. So for  
7 whatever it's worth.

8 DR. SMITH: So I'll add my statement, that  
9 in considering how to approach -- you look shocked,  
10 Dr. Vos.

11 DR. VOS: I'm not shocked. So was ALT  
12 monitoring recommended or not recommended? It's  
13 not.

14 DR. PUCINO: No. ALT monitoring was not  
15 recommended. Just signs and symptoms for the  
16 patient to report to us.

17 DR. SMITH: Dr. Vos, you're comfortable with  
18 that?

19 DR. VOS: Yes.

20 DR. SMITH: Yes. Dr. Wilson.

21 DR. W. WILSON: Just to be clear, not that  
22 that you've decided this, you were just going to be

1 putting in the toxicity section that you saw one  
2 episode. Right? You're not talking about a black  
3 box warning or anything like that?

4 DR. GUETTIER: We haven't discussed labeling  
5 yet, so we haven't decided anything on the label  
6 yet. This is just preliminary information from a  
7 consultant that was involved in reviewing the  
8 application, so at this point we haven't decided  
9 yet where this is going to go.

10 DR. W. WILSON: Well, I was just going to  
11 say that if something raises to the level of a  
12 black box warning, then I would think you would  
13 want to have monitoring of transaminases because  
14 even though there may not be -- if there is liver  
15 injury, you want to stop this drug. And you want  
16 to stop it before someone turns yellow.

17 To me, it's a little bit counterintuitive  
18 that if it does raise to a black box warning, you  
19 wouldn't recommend liver enzyme monitoring if you  
20 thought it was that critical because you would want  
21 to stop the drug if in fact you see the LFTs going  
22 up because that's exactly what happened here.

1           So there is the issue of predicting. But  
2       then once you have liver injury, LFTs do go up and  
3       you'd want to stop the drug. So that's the only  
4       point I was making. A black box warning to me  
5       means monitoring LFTs.

6           DR. ROSEBRAUGH: So let me just probe that a  
7       little bit. As I said, of course we haven't made a  
8       decision on the drug. But do you have  
9       recommendations of where you would put this type of  
10      information for this drug in what we have? And  
11      what is your level of concern about it?

12          DR. W. WILSON: Well, I'm a medical  
13      oncologist, so I would leave this to Dr. Vos.  
14      Because once the drug stopped there was recurrent  
15      issues, and it really does look like it's an  
16      immune-based issue, activation of immunity, it was  
17      either coincidental or not -- this patient did have  
18      increased LFTs coming in. So it certainly  
19      suggested that this was a preexisting condition.

20          I personally would definitely put it in the  
21      toxicity, of course, and I know you would. I don't  
22      think it raises to the level of a black box because

1 I think that means LFT monitoring. But Miriam  
2 would really be much more equipped to answer that.

3 DR. VOS: I would agree. I would not raise  
4 it to the level of a black box warning. The severe  
5 liver disease fortunately often presents with an  
6 elevated bilirubin, and I just double-checked, and  
7 this case did. So clinically, they should be  
8 identifiable by the patient noticing their eyes  
9 turning yellow or the physician reviewing that.

10 So screening many thousands of patients with  
11 liver enzymes with AST and ALT probably wouldn't be  
12 beneficial. It wouldn't help you pick up this case  
13 more quickly.

14 DR. SMITH: Is that okay from FDA  
15 perspective in terms of input? Okay. We'll move  
16 on to the next question, which is a voting  
17 question.

18 For the voting questions, we will be using  
19 an electronic voting system for this meeting. Once  
20 we begin the vote, the buttons will start flashing  
21 and will continue to flash even after you have  
22 entered your vote. That is the button on your

1 microphone.

2 Please press the button firmly that  
3 corresponds to your vote. If you are unsure of  
4 your vote or you wish to change your vote, you may  
5 press the corresponding button until the vote is  
6 closed.

7 After everyone has completed their vote, the  
8 vote will be locked in. The vote will then be  
9 displayed on the screen. The DFO will read the  
10 vote from the screen into the record.

11 Next, we will go around the room, and each  
12 individual who voted will state their name and vote  
13 into the record. You can also state the reason why  
14 you voted as you did. We will continue in the same  
15 manner until all questions have been answered or  
16 discussed.

17 So let me read the first voting question,  
18 and we'll discuss it before we vote.

19 In accordance with the FDA's guidance for  
20 industry titled "Diabetes Mellitus: Evaluating  
21 Cardiovascular Risk in New Antidiabetic Therapies  
22 to Treat Type 1 Diabetes," has the applicant

1 provided sufficient evidence that dapa, relative to  
2 comparators, has an acceptable cardiovascular risk  
3 profile? If you voted yes to this question number  
4 4, please provide your rationale. If you voted no  
5 to question 4, please provide your rationale.

6 Does anyone have comments or questions for  
7 clarification here before we proceed with the vote?

8 (No response.)

9 DR. SMITH: So we'll proceed with voting.

10 (Vote taken.)

11 DR. ABRAHAM-BURRELL: Okay. The results  
12 are, we have 10 that voted for yes, 4 that voted  
13 for no, and zero abstained.

14 DR. SMITH: So we'll start with Dr. Peter  
15 Wilson, and if you'll state your name into the  
16 microphone, your vote, and then if you'll comment  
17 on the rationale.

18 DR. P. WILSON: Peter Wilson. I voted yes.  
19 I thought that preponderance of the available  
20 information would suggest that this is a safe drug.  
21 I would like to see more information, but I thought  
22 that the sponsor had very adequately responded to

1 the directive that was put before them in 2011.

2 I would like to see more continuing safety  
3 information. But I believe the drug is safe for  
4 persons who have not had an event and also for  
5 those who have already experienced a CVD event.

6 DR. PACKER: I voted no. It's a question of  
7 what represents sufficient evidence. I think this  
8 kind of evidence is generally insufficient. I  
9 don't think this is the kind of quality that we  
10 should be making decisions about. I think the  
11 cardiovascular safety profile might be very benign,  
12 but I don't know. So I'm not prepared to say yes.

13 DR. MCBRYDE: I'm Kevin McBryde. I voted  
14 no. For similar reasons that Dr. Packer explained,  
15 I think that in high-risk diabetic patients, as  
16 demonstrated by studies 18 and 19, I think that  
17 there may be a concern that they are at increased  
18 risk for cardiovascular events, and the remaining  
19 studies did not relieve me of that concern.

20 I didn't see anything in the information  
21 that suggested that in fact they're going to try  
22 and exclude patients with hypertension,



1       cardiovascular disease, et cetera, from being  
2       treated with this drug. So I worry about the high-  
3       risk population and the risk of the events that  
4       were demonstrated in those two studies.

5               DR. SMITH: Thank you. Dr. Packer, I think  
6       you did not state your name. So if you would just  
7       activate your mic, state your name and your vote.

8               DR. PACKER: Packer. No.

9               DR. LEWIS: Julia Lewis. I voted yes. I  
10      looked at the question. It said, "In accordance  
11      with the FDA's guidance." I believe that the  
12      company consistently and across many different  
13      subgroups were in accordance with the FDA's  
14      guidance for cardiovascular risk assessment in  
15      diabetes studies. And I think the overall  
16      population, just being bigger and having more  
17      events, is the one that should help drive my  
18      decision.

19              DR. FOJO: Tito Fojo, and I voted yes for  
20      the very same reason. I thought that in accordance  
21      with FDA guidance that had been provided, and  
22      sufficient -- somebody's sufficient is another's

1       insufficient.

2               I think they provided substantial evidence,  
3       and at some level we almost have to speculate what  
4       might be wrong with the data that would cause us to  
5       think that the conclusions that we have with the  
6       data that we have is wrong. And so at this point  
7       I'm prepared to take the data at face value.

8               MS. BERNEY: Barbara Berney. I voted yes.  
9       After listening to all of the discussion -- this  
10      has been a real education for me -- I agree with  
11      Dr. Lewis. I have reservations about certain  
12      things, but on the balance of yes and no, I believe  
13      that they satisfied those things that were  
14      necessary to satisfy.

15              DR. BRITTAIN: Erica Brittain. I voted yes.  
16      I answered this question from the perspective of  
17      the guidance about excluding a relative risk  
18      greater than 1.8 and with the understanding that  
19      there would be a follow-up definitive study.  
20      Otherwise, I wouldn't have answered the question  
21      the same way.

22              So again, if the standard is 1.8, I think

1       it's clear there's sufficient evidence that that  
2       bar is met, no matter how I look at the data. And  
3       again, it's only a preliminary assessment, but at  
4       least the overall point estimate was positive in  
5       the overall population, which is at least somewhat  
6       promising. Of course, ultimately I hope that the  
7       outcome trial will show superiority, which is  
8       really the point, I think.

9               I do, however, agree that the issues that  
10       were raised about censoring are important and that  
11       it is important to do analyses both ways in terms  
12       of follow-up.

13              MS. HALLARE: Diana Hallare. I voted no,  
14       similar to Dr. Packer's response. And I was also  
15       considering the primary analysis results and the  
16       results within the first 30 days, particularly the  
17       adverse events.

18              DR. SMITH: I'm Robert Smith. I voted no,  
19       and this vote primarily derives from the words  
20       "sufficient evidence" in the voting question. I  
21       feel that the limitations in numbers of events, in  
22       some of the different subgroups that raise

1       concerns, and in terms of some of the aspects of  
2       the data that have been discussed by others, that I  
3       did not have a level of confidence that I would  
4       consider this sufficient evidence for compliance  
5       with the FDA guidelines.

6               On the other hand, I do understand that -- I  
7       don't feel tremendous concern about the  
8       cardiovascular risk signal. And so I would be  
9       comfortable with a postmarketing approach to this.  
10      So I didn't answer the question that way; I  
11      answered literally what I was asked.

12             DR. THOMAS: Abraham Thomas. I voted yes.  
13      I think, in terms of the guidance, there's  
14      sufficient information to decide that this drug can  
15      continue on potentially to marketing, if it's  
16      approved. The definitive trial that's already  
17      started in other parts of the world will really be  
18      the one to answer the question, once you have  
19      enough events and it's powered properly, do you see  
20      an absence of any risk.

21             DR. SMITH: Dr. Hiatt, if you could answer  
22      next.

1 DR. HIATT: Hiatt. I voted yes. I think I  
2 interpreted this question based on the guidance.  
3 And the point estimate and upper bound of 95  
4 percent confidence intervals were well below the  
5 thresholds required by the guidance.

6 But I'd like to note that I have residual  
7 concerns, very similar to the concerns expressed at  
8 the canagliflozin meeting earlier this year. I'm  
9 concerned about a class effect inducing early risk  
10 of cardiovascular events. But I think a  
11 cardiovascular outcome trial is required to  
12 evaluate that risk.

13 So I would like to say, linking these two  
14 drugs in the same class, that those concerns about  
15 cardiovascular risk have not been resolved by the  
16 current evidence and does require further study.

17 DR. SAVAGE: Peter Savage. I voted yes. I  
18 also thought that the sponsor had done a good job  
19 trying to provide additional information from the  
20 previous review and some of the questions that had  
21 been raised.

22 I think that we have to strike some sort of

1 a balance between the time we say a study of this  
2 sort can go ahead or when we get absolutely  
3 definitive clinical trial information. We'd slow  
4 the whole process of developing new drugs down  
5 dramatically for diabetes if we did that.

6 So I thought it complied with the FDA  
7 guidance. And I also expressed the concern earlier  
8 that the early events issue needs to be looked into  
9 because clearly, the numbers that we have are too  
10 small.

11 DR. VOS: Miriam Vos. I voted yes, for very  
12 similar reasons.

13 DR. W. WILSON: Wyndham Wilson. I voted  
14 yes. I felt that the sponsor had followed the FDA  
15 guidance, and I felt comfort at this point that  
16 there is not a sufficient cardiac adverse signal to  
17 warrant holding the drug up. But like everyone  
18 else, I think that this needs to be studied more  
19 carefully, and also whether or not there is an  
20 early 30-day increased rate of cardiac side  
21 effects.

22 DR. SMITH: Thank you. So we'll go on to

1 the last question, which is also a voting question.

2 Based on the information included in the  
3 briefing materials and presentations today, do the  
4 benefits of dapagliflozin use outweigh identified  
5 risks and support marketing of dapa as an adjunct  
6 to diet and exercise to improve glycemic control in  
7 adults with type 2 diabetes mellitus?

8 If you voted yes to question number 5,  
9 please provide your rationale and whether you  
10 recommend any additional studies post-approval. If  
11 you voted no to question 5, please provide your  
12 rationale and discuss what additional data are  
13 necessary to support approval.

14 Any questions? Clarifying questions or  
15 discussion points people would like to raise before  
16 voting?

17 (No response.)

18 DR. SMITH: Okay. We'll progress to the  
19 vote.

20 (Vote taken.)

21 DR. ABRAHAM-BURRELL: Okay. For question  
22 number 5, the results are 13 voted yes, 1 voted no,

1 and zero abstained.

2 DR. SMITH: So we'll start this time the  
3 other side of the room with Dr. Wyndham Wilson.  
4 If you'd read your name, your vote, and your  
5 rationale -- or, I'm sorry, your comments about  
6 either post- or premarketing studies.

7 DR. W. WILSON: Wyndham Wilson. I voted  
8 yes. I felt that based on my understanding, that  
9 the drug hit its surrogacy endpoints for being  
10 useful in diabetes.

11 I also felt that some of the negative  
12 aspects of this drug did not rise to the level of  
13 nonapproval for me. We've just discussed the  
14 cardiac. I have made my feelings known on the  
15 cancer risk, and I also feel that the hepatic risk  
16 also doesn't raise to the level of nonapproval.

17 Having said that, I think the postmarketing  
18 studies that are being planned and also underway  
19 are addressing the bladder cancer risk, breast  
20 cancer risk, cardiac risk, and they're clearly  
21 going to be reporting any liver side effects. But  
22 I don't know the details on that yet.



1 DR. VOS: Miriam Vos. I voted yes. I  
2 thought that the benefits that were consistently  
3 shown in the trials outweighed the risks for very  
4 similar reasons that Dr. Wilson just explained. I  
5 do think the postmarketing monitoring and the  
6 DECLARE trial is very important. And I didn't feel  
7 like there was anything additional to add.

8 DR. SAVAGE: Peter Savage. I voted yes,  
9 for essentially the reasons that have already been  
10 mentioned. I think that the risk appears to be low  
11 enough to go ahead, but there is surveillance  
12 that's needed to make sure that we're not missing  
13 something.

14 DR. THOMAS: Abraham Thomas. I voted yes.  
15 People have mentioned the trials that are already  
16 ongoing. I would just mention a few things that  
17 should be considered long-term.

18 One is the families that have these defects,  
19 they don't develop kidney disease, from what I  
20 remember reading, but they don't have diabetes. So  
21 I think there needs to be long-term observation for  
22 any decrease in kidney function, which hasn't been

1 really discussed beyond these trials, because the  
2 effects may be many years after taking these  
3 agents.

4 The second thing is, there's a big disparity  
5 in terms of elderly. More of the complications  
6 seem to be in the elderly, and then also those with  
7 a lower eGFR.

8 So for the elderly, I think there will have  
9 to be further understanding of what the risks are  
10 for, one, initiation and continuation of the agent  
11 specifically for things like hypotension and  
12 fractures.

13 So those might be other studies or follow-up  
14 that will need to be done to ensure safety in an  
15 elderly population that may not be there in a  
16 younger population.

17 DR. SMITH: I'm Robert Smith. I voted yes,  
18 for much of the reasons that have already been  
19 stated. I do feel that postmarketing studies would  
20 be important.

21 I think the DECLARE study includes  
22 substantially the things that one would want to

1 look at, most notably, cardiovascular events and  
2 malignancies. It appears to be a well-designed  
3 study, but of course there should be careful  
4 scrutiny and thought by the FDA if in fact they do  
5 approve this drug.

6 MS. HALLARE: Diana Hallare. I voted no  
7 since there may be potential risk for cancer, for  
8 infections, and also there may be increased  
9 cardiovascular risk as well. And therefore, I  
10 voted no.

11 DR. BRITTAIN: Erica Brittain. I voted yes.  
12 I voted no in 2011. As I indicated then, it was  
13 such a close call for me; it was pretty much a coin  
14 flip. And even though my official vote has  
15 changed, I wouldn't say my feeling has changed all  
16 that much because there hasn't been a lot of new  
17 information since then. Certainly the efficacy on  
18 the prespecified endpoints is really, really good  
19 and consistent. On the other hand, it is only a  
20 surrogate endpoint.

21 I do remain somewhat uneasy about the  
22 bladder cancer imbalance. But I guess my concerns

1       are somewhat lessened by the fact that there was  
2       only one additional event -- if I have that  
3       right -- just one new event when there was a lot of  
4       new follow-up, and that the cancer experts do not  
5       seem to think that it's very biologically  
6       plausible.

7               So I guess that tipped me to the other side  
8       of the fence. And I guess we still need to make  
9       sure that every precaution is taken as far as the  
10      cancer risk. I like the plan in DECLARE to monitor  
11      every 10 cases.

12             I guess the last point is that it's really  
13      critical that DECLARE get done and be finished.  
14      I'm voting contingent on the notion that it will be  
15      finished, and I guess that's my biggest concern,  
16      about whether it's going to be hard to recruit once  
17      the drug's approved. But please finish it.

18             MS. BERNEY: Barbara Berney. I voted yes,  
19      primarily for all of the reasons that have been  
20      stated. But also, as a patient who started out  
21      with A1c well over 7, now under 6 for quite a  
22      while, I can tell you it's a pain in the behind to

1 be vigilant and to be compliant to the point where  
2 you can really lower your A1c.

3 For patients who are not compliant, having  
4 something that they can take whenever -- oh, I  
5 forgot to take my meds today -- would be a real  
6 boon. I think also something that is very  
7 important, I got on metformin and lost 40 pounds.  
8 Started on glyburide in addition to that and gained  
9 10 pounds, which did not make me happy. But I have  
10 a good A1c, so I'm happy about that.

11 But all of these things suggest progress to  
12 me, and I'm encouraged by that. I also agree that  
13 the postmarketing assessment needs to be done and  
14 followed through because, as with anything else,  
15 there's risk. It would be nice to know that there  
16 weren't, but until we know that, you just have to  
17 use your best instinct. And that's what I did.

18 DR. FOJO: Tito Fojo, and I voted yes. And  
19 all of the reasons for it have already been covered  
20 by everybody.

21 The only thing I would add is I think we  
22 also need to realize this is a drug that's approved

1 in a lot of places already in the world. So at  
2 some point they've got a head start on us, so  
3 hopefully there will also be information that  
4 emerges from there that will valuable to us here in  
5 the United States.

6 DR. LEWIS: I'm Julia Lewis. I did vote  
7 yes. Probably, again, the thing that still  
8 disturbs me, although I am really reassured by both  
9 Dr. Wilson and Dr. Fojo, was the bladder cancer  
10 risk.

11 I'd like to make a somewhat unconventional  
12 suggestion, which is, the combination of diabetes,  
13 which is a risk factor for bladder cancer, and  
14 urinary tract infections and a microenvironment of  
15 infection and inflammation will exist in the class,  
16 probably.

17 There are, I believe, ongoing postmarketing  
18 studies with cana, and perhaps you could ask them  
19 to monitor bladder cancer in their postmarketing  
20 studies to better inform us about the class of  
21 agents, because we've got small numbers, and they  
22 could have fallen out any way. And cana didn't

1       turn out so bad, but we've got 14 to 5, if you look  
2       at both together. So perhaps you could do that.

3               DR. MCBRYDE: Kevin McBryde. I voted yes  
4       this time. Two and a half years ago I voted no. I  
5       feel more comfortable with the expertise on this  
6       advisory committee in terms of the cancer risks and  
7       the hepatotoxicity risks.

8               I continue to have concerns about  
9       cardiovascular risks with this drug, similar to  
10      what I had two and a half years ago. I was hoping  
11      for more information. Two and a half years ago I  
12      asked the sponsor about albuminuria in these  
13      patients because this is a highly protein-bound  
14      drug, and two and a half years later unimpressed to  
15      see that they haven't presented any information on  
16      that. So we don't know anything about diabetic  
17      nephropathy with proteinuria and the use of this  
18      drug.

19              So I still have significant concerns about  
20      the drug, mainly that just have been missed or  
21      ignored. But I think, with looking at the FDA  
22      guidance, I think going towards the postmarketing

1 study is important in terms of the cardiovascular  
2 risk. But I do feel that with the expertise here,  
3 I feel better about the hepatotoxicity and the  
4 cancer risk. So I voted yes this time.

5 DR. PACKER: Milton Packer. I voted yes. I  
6 actually really like this drug.

7 (Laughter.)

8 DR. PACKER: It's not strange, is it? No.  
9 It lowers hemoglobin Alc. Lowers blood pressure.  
10 Causes weight loss. All of these are good things.  
11 And I think that physicians will find a way to use  
12 it.

13 My concerns about cardiovascular safety and  
14 bladder cancer risk are still concerns. But we  
15 approve lots of drugs with uncertainties. We  
16 approve lots of drugs without knowing what's going  
17 to happen in the future.

18 It wouldn't be so uncomfortable to say that  
19 this drug by far passes the usual standard because  
20 the usual standard is filled with uncertainty. Do  
21 I have any doubts that DECLARE will be completed?  
22 I think DECLARE will absolutely be completed. It's



1       being done by the TIMI group, and you can see it's  
2       TIMI-58. There have been 57 previous TIMI studies.  
3       And my guess is they won't do others if they don't  
4       get this one done. So I have no doubt that they're  
5       going to get it done.

6               (Laughter.)

7               DR. PACKER: So the concerns that I raised  
8       were concerns based on principle, not concerns that  
9       we should limit the approval of this particular  
10      drug.

11              DR. P. WILSON: Peter Wilson. I voted yes.  
12      Let me just say a couple of things.

13              It reminds me of when I was in  
14      Massachusetts. When you approach a traffic circle,  
15      there's a flashing green light. And you proceed,  
16      but you proceed with not usual caution but some  
17      caution.

18              So in addition to the hematuria and the  
19      cancer risk, I fully feel that the DECLARE study  
20      will resolve the cardiovascular risk, very  
21      strongly. But I have two other concerns. One of  
22      them was mentioned indirectly by Dr. Thomas.

1           The first is the change over time with eGFR  
2   for diabetic patients. And many of these patients  
3   will be on metformin, and then they'll add dapa.  
4   And they may, as creatinine goes up, be on drugs  
5   that are no longer really that effective, and  
6   they're going to have to be watched.  
7   Endocrinologists are used to watching this.  
8   Nephrologists watch this. But as a physician  
9   group, we need to watch this for these drugs, for  
10   these patients.

11           Then finally, I think the signal potential  
12   for breast cancer is going to become a longer  
13   follow-up, and I'm not sure that will come out of  
14   the DECLARE study. And like some of our other  
15   pharmacovigilance for safety for breast cancer, it  
16   may be 5 to 10 years to really start to know that  
17   we're safe for that. Thank you.

18           DR. SMITH: Dr. Hiatt, your vote, please?

19           DR. HIATT: William Hiatt. I voted yes. I  
20   think, narrowly defined, it meets the surrogate A1c  
21   efficacy standard. And it also, I think, meets the  
22   FDA guidance on cardiac safety.

1           The comments on other safety risks I would  
2       agree with. The residual concerns have already  
3       been stated, and hopefully the cardiovascular  
4       outcome trial will solve that. Thank you.

5           DR. SMITH: Thanks. Does the FDA have any  
6       final comments you'd like to make?

7           DR. GUETTIER: We'd like to thank the  
8       sponsor, the FDA participants, and the panel  
9       members for a very lively discussion today. Your  
10      insights really help us in working through some of  
11      the complicated issues that, actually, you have  
12      brought up during your discussion. So thank you.

13          DR. SMITH: Dr. Lewis, did you have another  
14      question or comment?

15          DR. LEWIS: Renal didn't come up at all  
16      during our meeting, but it's come up twice in the  
17      comments. I'm not going to go on a diatribe  
18      because the deal is done. But I had no renal  
19      concerns, looking at it very, very carefully.

20                               **Adjournment**

21          DR. SMITH: Thank you. So I would like to  
22      thank the sponsor for your presentations and your

1 help in bringing data to us and explaining data  
2 today. I want to thank the FDA for the same, for  
3 helping us to understand the data and helping us to  
4 understand your questions so we could try to answer  
5 them.

6 Those who spoke at the open public hearing,  
7 I'd also like to thank you for your contributions,  
8 which we take very seriously. And thanks to the  
9 members of the advisory committee.

10 This meeting is adjourned.

11 (Whereupon, at 4:47 p.m., the committee was  
12 adjourned.)  
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