Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
January 10, 2013

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed new drug application (NDA) 204042, canagliflozin tablets, proposed trade name INVOKANA, submitted by Janssen Research and Development, LLC. Canagliflozin is a member of the sodium-glucose co-transporter 2 (SGLT2) inhibitors, and was developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

These summary minutes for the January 10, 2013 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on January 31, 2013.

I certify that I attended the January 10, 2013 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/Signed/

Caleb Briggs, PharmD
Acting Designated Federal Officer, EMDAC

/Signed/

Abraham Thomas, M.D., M.P.H.
Acting Chairperson, EMDAC

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
January 10, 2013

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on January 10, 2013. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products and posted on the Food and Drug Administration (FDA) website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/default.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA, Center for Drug Evaluation and Research, met on January 10, 2013 at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Janssen Research and Development, LLC. The meeting was called to order by Abraham Thomas, MD, MPH (Acting Chairperson), and the conflict of interest statement was read into the record by Caleb Briggs, PharmD (Acting Designated Federal Officer). There were approximately 150 people in attendance. There were five Open Public Hearing speakers.

Issue: The committee discussed new drug application (NDA) 204042, canagliflozin tablets, proposed trade name INVOKANA, submitted by Janssen Research and Development, LLC. Canagliflozin is a member of the sodium-glucose co-transporter 2 (SGLT2) inhibitors, and was developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):
Erica H. Brittain, PhD; David M. Capuzzi, MD, PhD; Edward W. Gregg, PhD

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present (Voting):
Vera Bittner, MD, MSPH; Ed J. Hendricks, MD; Ellen W. Seely, MD; Robert J. Smith, MD
Ida L. Spruill, PhD, RN (*Consumer Representative*)

Endocrinologic and Metabolic Drugs Advisory Committee Member Present (Non-Voting):
Mads F. Rasmussen, MD, PhD (*Industry Representative*)

Temporary Members Present (Voting):
Nakela Cook, MD, MPH, FACC; David W. Cooke, MD; William R. Hiatt, MD, FACP; Sanjay Kaul, MD; Rebecca Killion (*Patient Representative*); William C. Knowler, MD, DrPH, MPH, Julia B. Lewis, MD; David E. Malarkey, DVM, PhD, DACVP; Paul M. Palevsky, MD; Michael A. Proschan, PhD; Peter J. Savage, MD; Abraham Thomas, MD, MPH, FACP *(Acting Chairperson)*

FDA Participants (Non-Voting):
Jean-Marc Guettier, MDCM; Hyon (KC) Kwon, PharmD, MPH; Mary H. Parks, MD; Curtis J. Rosebraugh, MD, MPH; Mat Soukop, PhD

Acting Designated Federal Officer: Caleb D. Briggs, PharmD

Open Public Hearing (OPH) Speakers:
Kelly L. Close (diatribe); George Grunberger, MD, FACP, FACE (American Association of Clinical Endocrinologists); Paulina Duker, MPH, RN, BC-ADM (American Diabetes Association); Sidney M. Wolfe, MD (Public Citizen); Bennet Dunlap, MSHC

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Abraham Thomas, MD, MPH** Acting Chairperson, EMDAC
Conflict of Interest Statement	**Caleb D. Briggs, PharmD** Acting Designated Federal Officer, EMDAC
Introduction/Background	**Jean-Marc Guettier, MD** Diabetes Team Leader Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation (ODE-II) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**Janssen Pharmaceuticals, Inc.**
Introduction	**Jacqueline Coelln-Hough, RPh** Janssen Research & Development, LLC Senior Director, Global Regulatory Affairs
Medical Landscape & Unmet Need	**Edward Horton, MD** Senior Investigator, Joslin Diabetes Center, Boston Professor of Medicine, Harvard Medical School
Mechanism of Action, Phase 3 Program Overview, & Efficacy	**Gary Meininger, MD** Janssen Research & Development, LLC Franchise Medical Leader
Safety & Tolerability	**Peter Stein, MD** Janssen Research & Development, LLC Head of Metabolism Development
Benefit-Risk Review	**John Gerich, MD** Professor Emeritus, University of Rochester, New York

Clarifying Questions from the Committee

BREAK

FDA PRESENTATIONS

Canagliflozin: Clinical Efficacy and Safety	**Hyon (KC) Kwon, PharmD, MPH** Clinical Reviewer DMEP, ODE-II, OND, CDER, FDA
Canagliflozin: Statistical Assessment of CV Safety	**Mat Soukup, PhD** Team Lead Division of Biometrics 7 (DBVII) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA

Clarifying Questions from the Committee

LUNCH

Open Public Hearing Session

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Advisory Committee:

1) **Discussion:** Based on the information provided in the briefing materials and presentations at today's meeting, please weigh the benefit-risk profile of canagliflozin in the population of patients with type 2 diabetes and moderate renal impairment.

   In your discussion consider and comment on the following:

   - The impact of renal function on the glucose-lowering effect of canagliflozin
   - The impact of canagliflozin on the risk of renal function deterioration
   - The clinical importance of observed volume- and electrolyte- related changes associated with canagliflozin use to the overall safety of this population
   - The clinical importance of the observed increased risk of genitourinary tract infection associated with canagliflozin use to the overall safety of this population.

   Committee Discussion: The *committee members generally agreed that the benefit-risk profile of canagliflozin in patients with type 2 diabetes and moderate renal impairment should be considered differently from the general population. The committee members expressed concern about usage in these patients, owing to a decreased efficacy, especially*

when combined with an increased incidence of side effects. The committee members further discussed a discomfort with the relatively small volume of data to support use in this population. Some committee members did suggest a need for separate consideration of renal function in the elderly, as exclusion based only on eGFR could eliminate patients who may actually be suitable candidates for treatment with canagliflozin. One committee member also mentioned a concern over the cardiovascular risks of the drug, given an existing elevated cardiovascular risk in patients with renal impairment. Please see the transcript for details of the committee's discussion.

2) **Discussion:** In an analysis of clinical fractures across the Phase 3 development program, a numerical imbalance not favoring canagliflozin was seen in the incidence and in the exposure-adjusted incidence of fractures. The disparity appears to be driven by low-trauma upper limb fractures and to a lesser degree by spine fractures with little differences in lower limb, pelvis or rib fractures.

   Comment on the clinical significance of this finding on your overall assessment of safety.

   In your discussion consider the following:

   - The relevance of observed changes in calcium, phosphorus, parathyroid hormone and 1,25 dihydroxy vitamin D levels
   - The relevance of changes to bone turnover markers
   - The relevance of the bone mineral density changes at 52 weeks in the dedicated study in elderly individuals (DIA-3010)
   - The clinical importance of bone and calcium metabolism-related effect associated with canagliflozin use to the overall safety of this population and in the renally-impaired population

   Committee Discussion: *The committee agreed that the impact on bone could not be fully understood from the available data, and that a 52 week assessment likely does not provide sufficient information about this risk. One member suggested that long term studies may be necessary either before or post-marketing to assess the potential clinical impact of these changes. Another committee member suggested that the decrease in bone mineral density could be related to weight loss with canagliflozin, and that it may be expected to plateau. Also, another committee member noted a particular concern in the renally-impaired population, in which hyperphosphatemia and decreased 1,25 dihydroxy vitamin D can also be early features of renal osteodystrophy, and can lead to worse outcomes in this group of patients than in the general patient population. It was also discussed that there could be particular concern with off-label use of canagliflozin in non-type 2 diabetes in younger patients, where changes in bone density during these years could have a more detrimental impact over the course of life. Please see the transcript for details of the committee's discussion.*

3) **Discussion:** The cardiovascular risk associated with canagliflozin use was assessed in a prespecified meta-analysis of adjudicated cardiovascular events across nine Phase 2 and 3 clinical trials using a composite endpoint (MACE+) that combines cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina.

   Based on the information provided in the briefing materials and the presentations at today's meeting, please discuss the following:

   - Whether results based on the pre-specified Cox proportional hazards model are reliable.
   - Your level of concern regarding the apparent imbalance not favoring canagliflozin in early (< 30 days) MACE+ events observed in the dedicated cardiovascular outcomes trial (DIA-3008)
   - The divergence of risk estimates for the components of MACE+ in the prespecified meta-analysis in which the HR for nonfatal stroke exceeds 1.0 while the other components are below 1.0.
   - The clinical relevance of the observed changes to blood pressure, weight and low density cholesterol levels toward informing overall cardiovascular benefit/risk associated with canagliflozin use.

   NOTE: It was noted during the meeting that question #3 inaccurately states a hazard ratio for nonfatal stroke which exceeds 1.0. This hazard ratio actually applies to both fatal and nonfatal stroke.

   Committee Discussion: *Several committee members discussed their comfort in the reliability of the results of the pre-specified Cox proportional hazards model, though others did cite certain areas of concern, particularly with long-term impact. The committee generally agreed that long-term follow up would be necessary to properly assess the clinical relevance of changes in blood pressure, weight and low density cholesterol levels. The committee members also described some level of concern with the imbalance of MACE+ events at thirty days in the DIA-3008 trial, but many members reiterated that this was not a result of a pre-specified analysis, and encouraged caution in assigning too much significance to this occurrence. One member did question whether this could possibly be an indication of a subgroup with higher risk. One committee member stated that, because this drug acts as an osmotic diuretic, there could be a wider impact on the function of the kidneys than is easily understood. The committee members also discussed concern with the potential of type 1 error with an interim analysis in the cardiovascular outcomes trial and the need to balance this risk with the need to bring drugs to market more quickly. Please see the transcript for details of the committee's discussion.*

4) **Vote:** In accordance with FDA's Guidance for Industry titled "Diabetes Mellitus – Evaluating CV Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes", at the time of NDA submission, all applicants are to compare the incidence of important CV events occurring with their investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio is less than 1.8.

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

   Yes: 8 No: 7 Abs: 0

   a. If you voted "Yes" to question #4, please provide your rationale.

      Committee Discussion: *The committee members who voted "yes" generally expressed a concern with the relatively limited volume of data to inform this risk, and stated a desire for longer follow-up for cardiovascular endpoints. These members cited some unresolved questions, such as an increased incidence of stroke, increases in low-density cholesterol, and imbalanced MACE+ events at thirty days. These members generally discussed a need for a longer period of exposure, particularly for a drug that treats a chronic disease. Please see the transcript for details of the committee's discussion.*

   b. If you voted "No" to question #4, please provide your rationale.

      Committee Discussion: *The committee members who voted "no" did not differ significantly from the perspective of those who voted "yes". These members expressed some level of concern over the increased stroke incidence, low-density cholesterol, and MACE+ events at thirty days, but described a general comfort with the data overall. These committee members also described a desire for more data to help inform the cardiovascular risks, but stated that the currently-available data is not especially alarming. Please see the transcript for details of the committee's discussion.*

5) **Vote:** Based on the information included in the briefing materials and presentations today, has the applicant provided sufficient efficacy and safety data to support marketing of canagliflozin for the treatment of Type 2 diabetes mellitus?

   Yes: 10 No: 5 Abs: 0

   a. If you voted "Yes" to question #5, please provide your rationale and whether you recommend any additional studies post-approval.

      Committee Discussion: *The committee members who voted "yes" expressed confidence in the efficacy data, as well as the promise of a new mechanism of action which is not dependent on insulin. Some committee members cited strong results on the primary endpoint. One member specifically cited a positive impact for patients, with weight loss*

and limited hypoglycemia. Those committee members who voted "yes" consistently expressed a remaining desire for further study of cardiovascular effects, especially in longer term exposure. Several members also described a concern over usage in patients with moderate renal impairment, with many mentioning that their support for a favorable benefit-risk profile did not extend to these patients. Those committee members frequently stated that the drug labeling should reflect concerns in these patients. Please see the transcript for details of the committee's discussion.

b. If you voted "No" to question #5, please provide your rationale and discuss what additional data are necessary to potentially support approval.

Committee Discussion: *The committee members who voted "no" cited similar concerns over unknown cardiovascular risk and usage in moderate renal impairment, which were frequently stated as overriding concerns. One committee member who voted "no" expressed comfort with the benefit-risk profile in combination therapy, but described a lack of comfort with usage as monotherapy since the drug had not been compared against metformin, which is the standard initial therapy in Type 2 diabetes. An additional committee member voiced concerns over the potential for renal damage, and suggested a possibility of prolonging hypoglycemia in the elderly. Please see the transcript for details of the committee's discussion.*

The meeting was adjourned at approximately 4:30 p.m.