FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
FDA White Oak Campus, Building 31, The Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland

January 10, 2013

DRAFT QUESTIONS TO THE COMMITTEE (cont.)

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1) **DISCUSSION:** The cardiovascular risk associated with canagliflozin use was assessed in a prespecified meta-analysis of adjudicated cardiovascular events across nine Phase 2-3 clinical trials using an endpoint 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 whether you believe the applicant has provided sufficient evidence of cardiovascular safety to support marketing of canagliflozin.

   In your discussion address the following specific points:

   - Whether results based on the pre-specified Cox proportional hazards model are reliable.
   - 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.
   - 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 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.

2) **DISCUSSION:** Based on the information provided in the briefing materials and presentations at today's meeting, do you believe the potential benefits of canagliflozin outweigh its potential risks when used in a 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.
   - The clinical importance of bone and calcium metabolism related effect associated with canagliflozin use to the overall safety of this population

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3) **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 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 benefit risk balance.

   In your discussion consider the following:

   - The relevance of observed changes in calcium, phosphorus, parathyroid hormone and 1,25 dihydroxy vitamin D levels to this finding
   - The relevance of changes to bone turnover markers to this finding
   - The relevance of the bone mineral density changes to 26-weeks in the dedicated study in elderly individuals (DIA-3010) to this finding

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", has the applicant provided sufficient evidence that canagliflozin, relative to comparators, is not associated with an unacceptable CV risk profile.

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

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

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?

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

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

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