FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
Hilton Washington DC/Rockville Hotel & Executive Meeting Center, Plaza Ballroom
1750 Rockville Pike, Rockville, Maryland
June 28, 2016

DRAFT QUESTIONS

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1. **DISCUSSION:** Discuss your interpretation of the EMPA-REG OUTCOME study conduct. Please comment on whether interim unblinding or changes made to the protocol, endpoint definitions, and analyses plan (e.g., specific exclusion of silent MI from the primary endpoint) during the course of the EMPA-REG OUTCOME study alter or do not alter your level of confidence in a conclusion that excess CV-risk was excluded and CV-benefit was established.

2. **DISCUSSION:** Discuss your interpretation of the nonfatal components in the composite endpoint (i.e., nonfatal myocardial infarction and nonfatal stroke) in relation to the overall results. Please comment on the non-fatal myocardial infarction findings in the EMPA-REG OUTCOME study and your level of concern related to potentially incomplete ascertainment of some myocardial infarction events (i.e., silent MI) in this trial. Please comment on the non-fatal stroke findings in the EMPA-REG OUTCOME study.

3. **DISCUSSION:** Discuss your interpretation of the mortality findings in the EMPA-REG OUTCOME study in relation to the overall results. Please comment on your level of confidence in the mortality findings. In your discussion, please address any potential limitations of these data including but not limited to:

    a. The divergent effect on the fatal and non-fatal components for the primary major adverse cardiovascular event (MACE) endpoint

    b. The proportion of deaths that were determined "non-assessable" by adjudicators

    c. The lack of granular data on potentially important information such as baseline heart failure history and dose of relevant baseline and concomitant medications

4. **DISCUSSION:** Discuss the heart failure findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on heart failure and heart-failure related outcomes.

5. **DISCUSSION:** Discuss the renal findings in the EMPA-REG OUTCOME study. Please comment on the potential limitations of these data, if any, and on whether the results of the study establish a benefit of empagliflozin on kidney disease related to diabetes.

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DRAFT QUESTIONS (cont.)

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6. **VOTE:** Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results have fulfilled the recommendations laid out in the 2008 Guidance for Industry by demonstrating that use of empagliflozin to improve glycemic control would not result in an unacceptable increase in cardiovascular risk?
    a. If yes, please provide the rationale for your vote.

    b. If no, please provide the rationale for your vote and comment on what additional data would be needed.

7. **VOTE:** Based on data in the briefing materials and presentations at today's meeting, do you believe the EMPA-REG OUTCOME study results provide substantial evidence to establish that empagliflozin reduces cardiovascular mortality in the population studied?

    a. If yes, please provide the rationale for your vote.

    b. If no, please provide the rationale for your vote and comment on what additional data would be needed.

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