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

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:** Please discuss the persuasiveness of the statistical results for the primary analysis. Please also comment on how results for the individual components in the primary composite endpoint impact your level of confidence in the study findings. Finally, comment on concerns you may have related to potentially incomplete ascertainment of some myocardial infarction events (i.e., silent MI) in this trial and whether these concerns, if any, alter your level of confidence in the results for the primary analysis.

3. **DISCUSSION:** Discuss the persuasiveness of the mortality findings in the EMPA-REG OUTCOME study. In your discussion, please address any potential limitations of these data including but not limited to:

    - Issues raised in Discussion Point #2
    - The proportion of deaths that were determined "non-assessable" by adjudicators
    - The lack of granular data on potentially important information such as baseline heart failure history and dose of relevant baseline and concomitant medications
    - The lack of pre-specified alpha-adjustment for this endpoint

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.

QUESTIONS (cont.)

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.