# Endocrinologic and Metabolic Drugs Advisory Committee

April 1, 2009

QUESTIONS TO COMMITTEE

# CARDIOVASCULAR SAFETY
## Points for Discussion

1. Please discuss whether the low cardiovascular event rate in the saxagliptin clinical trials permits a reliable assessment of cardiovascular safety.

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2. Under the recent Guidance regarding evaluation of cardiovascular risk for diabetes therapies, ongoing and future diabetes drug development programs will be required to conduct preplanned adjudication of cardiovascular events, and to collect all data necessary for such adjudication. However, the saxagliptin development program was already complete by the time the guidance was issued. For saxagliptin, neither preplanned nor post-hoc adjudication occurred, and full data were not available to permit meaningful assessment of many cardiovascular events.

# CARDIOVASCULAR SAFETY
## Question 2 (cont.)

The “SMQ MACE” and “Custom MACE” endpoints were defined post-hoc for a drug development program that was not designed to prospectively measure cardiovascular risk associated with saxagliptin. Please discuss whether these endpoints and the post-hoc analyses permit a reliable assessment of cardiovascular safety. Please offer suggestions for improvements to the endpoints and analyses that may be applied to other diabetes programs that have already completed or had ongoing Phase 3 programs at the time the Final Guidance was issued.

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3. The saxagliptin trials included a 24-week, short-term, double-blind period followed by a long-term, double-blind period. Patients entered the long-term period if they completed the short-term period or if they were discontinued from the short-term period due to inadequate glycemic control. Patients who entered the long-term period because of inadequate glycemic control during the short-term period were administered open-label rescue medication. Please discuss whether this trial design affects interpretation of cardiovascular results for the short-term period and for the combined short-term and long-term periods.

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4. Multiple statistical methods were used to analyze cardiovascular outcomes. Please discuss the adequacy of these methods for measuring sensitivity of the results to analytical method.

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## Question 1 (voting)

Based on the preceding discussion, has the applicant provided appropriate evidence of cardiovascular safety to conclude that saxagliptin rules out unacceptable excess cardiovascular risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?

**(VOTE) Yes/No/Abstain**

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## Question 1 (cont.)

If voting "**No**" to Question 1, what additional cardiovascular data are needed to address any limitations resulting from the completed clinical development program and to support approvability, including satisfying the 1.8 non-inferiority margin?

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## Question 2 (voting)

For the Custom MACE endpoint, the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratio was less than 1.3. These data involved a total of 11 cardiovascular events in the 24-week, double-blind, short-term study periods and a total of 40 cardiovascular events in the combined short-term and long-term study periods of median 62-week exposure. Are these data adequate to conclude that post-marketing cardiovascular safety trial(s) are unnecessary? **(VOTE) Yes/No/Abstain**

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## Question 2 (cont.)

If voting "**No**" to Question 2, please comment on the limitations of the completed NDA program that will require an additional post-marketing trial(s).