**Endocrinologic and Metabolic Drugs Advisory Committee**
**April 2, 2009**

# LIRAGLUTIDE ADVISORY COMMITTEE MEETING
# APRIL 2, 2009

## CARDIOVASCULAR SAFETY

## POINTS FOR DISCUSSION

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

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 liraglutide development program was already complete by the time the guidance was issued. For liraglutide, neither preplanned nor post-hoc adjudication occurred, and full data were not available to permit meaningful assessment of many cardiovascular events. 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 liraglutide. 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.

3. In the cardiovascular event analyses, comparators of all active control, all add-on placebo control, and total comparator were used. Results were qualitatively similar for liraglutide vs. total comparator, and liraglutide vs. active comparator. However, comparisons to placebo were sensitive to analytical method, often yielded point estimates >1 (not favoring liralutide) and often yielded 95% confidence interval upper bounds of >1.8. Analyses were stratified by study, and lower baseline risk did not appear to contribute. Please discuss the relevance of these differences noted by type of comparator to the liraglutide program, and the role of these separate types of comparators in the evaluation of the cardiovascular risk for future diabetes drug applications.

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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## QUESTIONS

1. Based on the preceding discussion, has the applicant provided appropriate evidence of cardiovascular safety to conclude that liraglutide 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 requested)**

    a. If "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?

## THYROID TUMORS

## POINTS FOR DISCUSSION

1. Please comment on whether the applicant has provided adequate data that treatment-related thyroid C-cell tumors in carcinogenicity studies of liraglutide are rodent-specific and not clinically relevant to humans. Include calcitonin findings from clinical trials in your discussion.

2. Please comment on the numerical imbalance of reports of papillary thyroid cancer in the clinical trials.

3. Please discuss recommendations for clinical trial monitoring for thyroid C-cell tumors in the development programs for other GLP-1 analogs.

## VOTING QUESTIONS

1. Do the available data on thyroid C-cell tumors show that this finding is not relevant to humans? **(VOTE requested)**
    a. If voting "Yes", why?
    b. If voting "No", why not?

2. Assuming the remainder of the risk:benefit data are acceptable, do the available data on thyroid C-cell tumors permit approvability of liraglutide? **(VOTE requested)**
    a. If voting "Yes", why? Please comment on the need for and approach to post-approval risk management (e.g., whether baseline assessment and/or ongoing monitoring for medullary thyroid cancer is needed for liraglutide-treated patients. If so, what types of assessments should be done?)
    b. If voting "No", why not? What additional data related to medullary thyroid cancer are needed to support approvability?

3. Assuming the remainder of the risk:benefit data are acceptable, do the available data on papillary thyroid cancer permit approvability of liraglutide? **(VOTE requested)**
    a. If voting "Yes", why? Please comment on the need for and approach to post-approval risk management (e.g., whether baseline assessment and/or ongoing monitoring for papillary thyroid cancer is needed for liraglutide-treated patients. If so, what types of assessments should be done?)
    b. If voting "No", why not? What additional data related to papillary thyroid cancer are needed to support approvability?