**FOOD AND DRUG ADMINISTRATION**
Center for Drug Evaluation and Research

***Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee***
FDA White Oak Campus, Building 31, The Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland
October 17, 2011

## Questions to the Committee

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1) Please discuss whether the randomized start design, appropriately designed and conducted, is capable of detecting a disease modifying effect for treatment of patients with Parkinson's Disease? If not, are there alternative designs that can demonstrate such an effect?

2) Agency reviewers have identified numerous issues related to the analyses/results of ADAGIO (**A**ttenuation of **D**isease Progression with **AGI**LECT®/AZILECT® **O**nce Daily) and TEMPO (**T**VP-1012 in **E**arly **M**onotherapy for **P**arkinson's Disease **O**utpatients), including:
    a. Non-linearity of slopes, presumably related to varying early effects of treatment
    b. Re-analyses of slopes without early data suggest parallel slopes in Phase 1 for drug and placebo
    c. Potentially significant baseline differences in UPDRS (Unified Parkinson's Disease Rating Scale) scores between ES (early start) and DS (delayed start) patients in the Hypothesis 2 & 3 datasets, and potential biases in the analyses that compare these non-randomized groups
    d. Differential response in men and women (primarily in ADAGIO), and baseline differences in early and delayed women starters in ADAGIO
    e. Sponsor-conducted analyses that differed from those specified in the protocol

    Please discuss the impact these issues, as well as any other issues you consider important, have on your interpretation of the studies submitted.

3) Does ADAGIO provide compelling evidence that the 1 mg dose of rasagiline met the protocol specified criteria for success? **(voting question)**

4) The 2 mg dose failed to show a differential effect between the early and delayed starters at the end of the study. The sponsor has offered some explanations (e.g., patients in the worst quartile of baseline UPDRS scores seemed to have a better response than other patients). Did the 2 mg group fail to meet the protocol specified criteria for success? **(voting question)**

5) Has the sponsor provided substantial evidence of effectiveness for rasagiline as a treatment to delay clinical disease progression in patients with Parkinson's Disease? **(voting question)**