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

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
Hilton Washington DC North/Gaithersburg, The Grand Ballroom
620 Perry Parkway, Gaithersburg, MD 20877
June 9, 2015

DRAFT QUESTIONS

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1. **DISCUSSION:** Discuss the safety of alirocumab as observed in the clinical development program, and in your discussion comment on the following:

    a. Discuss your interpretation of the safety data with respect to any adverse effects related to diabetes, liver-related safety, muscle, neurological/neurocognitive events, hypersensitivity, immunogenicity, as well as any other concerns you may identify.
    b. Discuss the adequacy of the current clinical database to characterize the safety of alirocumab. Consider the extent of drug exposure (i.e., number of patients and duration of exposure), the strengths/limitations of the study designs themselves, and the generalizability of the trial populations to the target population(s), if approved.
    c. Discuss your level of concern regarding the safety of achieving very low levels of LDL-C induced by alirocumab.

2. **DISCUSSION:** The goal of LDL-C-lowering therapy is to reduce the risk of cardiovascular (CV) disease. Historically, a change in LDL-C has been considered sufficient to establish the effectiveness of a lipid-altering drug intended for use to reduce cardiovascular risk, without any regulatory requirement to demonstrate evidence for benefit in a CV outcomes trial, provided the reduction is sufficiently robust and the product (or its class) does not have safety issues that raise concern that risk exceeds benefit.

    Discuss whether alirocumab-induced LDL-C lowering is sufficient to substitute for demonstrating its effect on clinical outcomes (i.e., to substitute for investigation in a CV outcomes trial) in one or more populations (e.g., different degrees of CV risk, familial vs. non-familial etiologies of hyperlipidemia, use with or without concomitant statins, etc.).

3. **VOTE:** Has the applicant sufficiently established that the LDL-C-lowering benefit of alirocumab exceeds its risks to support approval in one or more patient populations? We remind you that under the current regulatory pathway, it would not be required to successfully demonstrate an effect of alirocumab on CV outcomes after an approval based on changes in LDL-C.

    a. If yes, please explain your rationale and describe the patient population(s) for whom you believe that the benefit/risk is favorable.
    b. If no, please describe what further studies you believe the applicant must conduct to establish a favorable benefit/risk to support approval.