# Endocrinologic and Metabolic Drugs Advisory Committee

Meeting on safety and efficacy of alirocumab

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I have no conflicts of interest

# Editorial published concomitantly with alirocumab and evolocumab studies

**"Because PCSK9 inhibitors allow the achievement of lower LDL cholesterol levels than those achieved to date with statins, a close look at safety is a paramount consideration."**

**"it would be premature to endorse these drugs for widespread use before the ongoing randomized trials, appropriately powered for primary endpoint analysis and safety assessment, are available. Reports from several lipid treatment trials provide important object lessons in this regard"**

**"specific assessment of neurocognitive function is needed"**

**ACC/AHA guidelines for possible use of non-statins "with a strong preference for use of non-statins that have been determined to be safe and effective in randomized, controlled trials"**

**Stone NJ, Lloyd-Jones DM. *NEJM* 2015 16;372(16):1564-5 (both members of ACC/AHA guideline task force)**

# FDA Concerns from briefing documents

"The unexpected and disappointing results from CV outcomes trials for fenofibrate,[1,2] cholesteryl ester transfer protein (CETP) inhibitors,[3,4] and niacin[5,6],…..should at least give us pause as we consider the use of lipid biomarkers in the assessment of benefit/risk"

"The proportion of patients meeting the criteria for diabetes diagnosed either by adverse event or laboratory value was 3.2% in the alirocumab group and 2.2% in the placebo group."

"We have concerns that many patients who have symptoms that may be entirely unrelated to statins could prematurely discontinue their statins and turn, instead, to a PCSK9 inhibitor, which will lack long-term safety data and CV outcomes."

# Recent Non-Statin LDL-Lowering Drug Trials

| Study | Total Patients | Duration | Major CV events |
|---|---|---|---|
| **Odyssey long-term*** | **2341** | **1.5 years** | **53-post-hoc** |
| **Odyssey outcomes**** | **18,000** | **2-5 years ****** | **1623-planned** |
| **Improve-It (ezetimibe)***** | **18,000** | **~5 years ******** | **5250** |

* Published this year (alirocumab) :
** Planned completion, 2018 (alirocumab)
*** Published this year, not-FDA evaluated
**** Until the # of pre-specified events are accrued

# Conclusions

- There may well be people who might benefit from the additional LDL cholesterol-lowering of the PCSK9 inhibitors.
- But at this time, the inadequate evaluation of a large enough number of patients over a long enough time, with pre-specified evaluation of cardiovascular outcomes and other safety concerns does not provide information for the necessary, evaluable benefit-risk balance.
- In the absence of such critical information, any approval at this time would, essentially, be a premature endorsement for widespread use.