Testimony to the Meeting of FDA's Endocrinologic and Metabolic Drugs Advisory Committee

Evolocumab (Repatha) BLA 125-522

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(We have no financial 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"

Referred to 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"

In addition, "specific assessment of neurocognitive function is needed"

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

FDA concerns from June 9, 2015 Briefing Documents (for alirocumab)

"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"

"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
OSLER-1 and 2* (evolocumab)	4,465	1 year	60-exploratory
FOURIER** (evolocumab)	27,500	5 years	1,630-planned
IMPROVE-IT (ezetimibe)***	18,144	6 years	5,250

* Published this year
** Planned completion 2018
*** Published this year, not-FDA evaluated

Other Non-Statin Drug Trials: LDL efficacy vs. CV benefit

Study	Total Patients	Duration	LDL decrease (comparator-adjusted)	Major CV events vs. comparator (HR/OR; 95% CI)
ILLUMINATE (torcetrapib)	15,067	1.5 years	27.9%	1.25 [1.09-1.44]*
HPS2-THRIVE (niacin)	25,673	3.9 years	16%	0.96 [0.90-1.03]
AIM-HIGH (niacin)	3,414	3.0 years	6%	1.02 [0.87-1.21]
ACCORD (fenofibrate)	5,518	4.7 years	NS**	0.92 [0.79-1.08]
dal-OUTCOMES (dalcetrapib)	15,871	2.5 years	NS**	1.04 [0.93-1.16]

* Terminated early; increase in all-cause mortality vs. statins alone (1.58; [1.14-2.19])

** No significant effect on LDL reduction; significant effect on HDL increase

Cardiovascular efficacy – including as add-on to statin therapy –unknown until FOURIER completion in 2018

Difference in major CV outcomes in exploratory analyses in OSLER-1 and 2 driven mostly by coronary revascularization, within the context of an unblinded trial.

"…the decision to perform this procedure could have been influenced by knowledge of treatment assignment." (Sabatine; N Engl J Med2015; 372:1500-9.)

Displacement of statin therapy: statin "intolerance"

"FDA reconfirmed [to the sponsor] that the FDA is unlikely to consider a monotherapy indication or an indication explicitly referencing 'statin-intolerant' patients without positive outcomes data…

…One possible unintended consequence of including a statin-intolerant indication or claim in the label is that statin-intolerance as a clinical entity will likely be promoted and marketed."

- FDA Clinical Reviewer, p. 51, 59

Statin “Intolerance”

“For the statin-intolerant population, the applicant chose not to use the Division’s working definition of statin intolerance [at the lowest starting dose of at least one statin].”

- FDA Medical Officer, p. 163

An overly lax definition of statin “intolerance”, as used in pre-approval trial 116, would make even more likely the potential displacement of appropriate statin therapy post-approval.

HoFH

- Evolocumab not studied against, and achieved only one half of the historical LDL-lowering effect of, apheresis, the most effective current therapy
  - LDL reduction: evolocumab 23%, apheresis 50%

- Only 1 of 49 subjects in HoFH trial was LDLR-negative/negative – and achieved no LDL reduction with evolocumab.
- "[I]t is likely that treatment of the entire HoFH population – where assessment of genetic mutations and their functional significance is not widely performed or understood – would yield a lesser treatment effect, on average."

  - FDA Clinical Reviewer, p. 184

Conclusion

Approval of evolocumab would add to the already considerable list of agents currently on the market which, like evolocumab, are effective in reducing LDL levels, but which have no evidence (or have evidence against) demonstrating long-term CV benefit.

Awaiting the results of the ongoing FOURIER trial would ensure that this does not happen, while setting a new precedent for the approval of LDL-lowering agents on the basis of actual CV benefit.