FDA Advisory Committee Supports Cardiovascular Safety Study Requirement - July 2, 2008

The FDA Endocrinologic and Metabolic Drugs Advisory Committee voted 14 to 2 in favor of requiring all new type 2 diabetes drugs to demonstrate cardiovascular safety in a hard outcomes clinical trial or by other means, even if no concerning cardiovascular signal is observed in phase 2/3. We believe that this has the potential to negatively influence diabetes drug development, although the degree to which diabetes drug development is impacted largely depends on exactly what version of the many proposals discussed is eventually implemented by the FDA.

The most widely accepted cardiovascular trial proposal amongst the panel members was some sort of a hybrid pre-approval "screening" trial/post-approval "confirmation" trial. The screening trial could possibly involve 2,500 patients (1,250 in study arm, 1,250 in control arm) followed for approximately 2.5 years to rule out with 95% confidence a cardiovascular hazard ratio of 1.8 or above (point estimate of ~1.5). The confirmation trial would be somewhat larger or longer in order to rule out a lower hazard ratio, although drugs displaying cardiovascular benefit in the screening trial might be exempted from a confirmation trial requirement.

Panelists for the most part agreed that a similar requirement should also be applied to all existing, non-generic type 2 diabetes drugs. If implemented, manufacturers of currently marketed diabetes therapies may need to conduct a post-marketing cardiovascular safety study of similar scale.

The vote reflected general consensus amongst the panelists that at the present time the FDA does not have enough data to rule out cardiovascular harm with new diabetes drugs. The vote is somewhat of a paradigm shift from the way diabetes drugs are currently approved; the FDA only currently requests long-term cardiovascular trials for a drug when there is a concerning cardiovascular safety signal in phase 2/3.

Below is a more specific rundown on the various proposals that surfaced at the meeting, our opinion of the decision, possible implications for diabetes drug development, and other key takeaways.

- **The panelists were in agreement that the FDA should use an independent blinded adjudication committee to monitor cardiovascular events for diabetes drugs.** The panelists expressed hope that this would lead to the standardization of cardiovascular adverse event reporting and other aspects of clinical trial design, in order to provide better information to the FDA. The panelists highlighted that an adjudication committee with clearer standards for reporting cardiovascular events and other adverse events would allow better analyses of data without impeding drug development.
- **If phase 2/3 trials were better standardized, panelists expressed hope that meta-analysis of safety data from the phase 2/3 trials would be more revealing in regards to cardiovascular risk and unexpected complications.** Several members of the panelunderscored that the lack of standardization in the rosiglitazone (Avandia) phase 2/3 clinical trials made it difficult to assess that drug's effects on cardiovascular risk.
- **The panelists also were generally in agreement that the FDA should require more robust phase 2 and phase 3 clinical trials**, because they felt that the current safety database is inadequate. The panelists justified their position by pointing out that mortality and complication rates for people with diabetes have fallen over the past 10-20 years, and therefore the safety hurdle for new drugs should be increased to ensure that the new drug is not doing more harm than good. No specific recommendations were produced by the committee, aside from several presenter comments noting that phase 2/3 clinical trials should include more high-risk patients. The consensus about a need for larger phase 2/3 clinical trials preceded the panel's discussion about a

cardiovascular safety study; presumably a cardiovascular safety study would fulfill the panel's desire for more robust pre-approval clinical data.

- **The panelists unanimously agreed that diabetes drugs should not be required to show cardiovascular benefit.** Echoing statements made by Dr. David Nathan in his presentation on day 1 of the conference, panelists mentioned that diabetes and cardiovascular disease are truly separate disorders. Therefore, they believed that it would be appropriate to approve a diabetes drug that does not cause cardiovascular benefit but is effective at lowering A1c, so long as the drug is safe. Several panelists underscored that cardiovascular benefit has not been demonstrated for any of the currently available therapies (except possibly metformin monotherapy in the UKPDS), and therefore it would be unreasonable to expect all new drugs to produce cardiovascular benefit.
- **There was a near-consensus among the panel members that the FDA does not currently have enough data to rule out cardiovascular harm with new drugs for type 2 diabetes - drugs for type 1 diabetes were not the subject of this panel discussion**. Most panelists said that a cardiovascular outcomes clinical trial should therefore be required for all new drugs, including new drugs without a concerning cardiovascular safety signal in phase 2/3. The vote in favor of a cardiovascular study requirement was 14-2; dissenters included a pediatric endocrinologist (Dr. Eric Felner) and, notably, the only patient advocate on the panel (Rebecca Killion).
- **Panelists agreed that the cardiovascular safety study requirement should apply to all drugs within a class, not only first-in-class drugs.** Panelists were apparently impressed by a slide presented by Dr. Steven Nissen demonstrating the large differences in gene activation by the currently and formerly approved PPARs. Dr. Nissen's argument was that within the TZD class, every drug is truly unique and may have a differentiated cardiovascular effect. We believe that the TZD class is somewhat unique in this respect, and given the mechanisms involved, the idea that all GLP-1s or DPP-4 or SGLT-2 inhibitors may carry different cardiovascular risks is misguided. The cardiovascular study requirement is likely to eventually appear ridiculous when the sixth DPP-4 inhibitor comes to the FDA advisory panel with 2,500-person cardiovascular data that looks super-imposable to every other five approved DPP-4 inhibitor.
- **There was less of a consensus about what kinds of cardiovascular studies the FDA should require, and what level of potential cardiovascular risk is acceptable for diabetes drug approval.** Panelists were divided about whether the cardiovascular study a study should be conducted pre-approval or post-approval, or some type of "hybrid" approach involving a pre-approval "screening study" followed by a "confirmatory trial."One proposal by Dr. Thomas Fleming that was generally well received was that drugs should be required to rule out with 95% confidence a cardiovascular hazard ratio of 1.8 or above (point estimate of ~1.5) in a single randomized pre-approval trial. This screening trial would require approximately 125cardiovascular events. Assuming a population with a baseline 2% per year rate of cardiovascular disease/ myocardial infarction/stroke, this would translate to approximately 2,500 patients (1,250 in study arm, 1,250 in control arm) followed for approximately 2.5 years. This trial would enable drugs to show absence of cardiovascular toxicity, or to show cardiovascular benefit. If this screening trial requirement were implemented, it would prevent six of seven drugs with a hazard ratio of 1.5 from being approved. The screening trial could then be followed by a confirmatory trial, to rule out a lower hazard ratio of approximately 1.333 (such a trial might require approximately 5,000 participants followed for five years).
- **The FDA received less clarity from the advisory panel than it had likely expected or hoped for.** The advisory panel was expected to provide a yes/no vote to the following question: "For those drugs or biologics without [a concerning cardiovascular safety signal], should there be a requirement to conduct a long-term cardiovascular trial?" However, panelists demanded more wiggle room, and the question was eventually reworded before the final vote to say: "For those drugs or biologics without a concerning cardiovascular signal, should there be a requirement for a long-term cardiovascular clinical trial *or to provide equivalent evidence from other sources to rule out an*

unacceptable cardiovascular risk?" Therefore, at face value the 14-2 vote in favor of the above statement does not necessitate a cardiovascular safety study. Nonetheless, it is hard to imagine that the FDA will be able to rule out "an unacceptable cardiovascular risk," even for a drug that produces cardiovascular benefit, without greatly expanding the clinical trial requirements.

- **Panelists generally agreed that all approved non-generic drugs should undergo a similar cardiovascular safety assessment.** The panelists suggested that it would be inconsistent not to require approved agents to fulfill the same cardiovascular hurdle as new drugs. In our view, it is inconsistent to allow generic drugs to go untested - although admittedly it is unclear who would pay for such clinical trials of generic drugs. The only class of drug that has demonstrated cardiovascular toxicity is the sulfonylureas, and they would be excluded from such a clinical trial requirement.
- **The devil is in the details, and to get the details we will need to wait for the FDA's response to the panel's recommendations.** Although it is possible that the FDA will reject the panel's suggestion of a cardiovascular safety study requirement entirely, we believe this is highly unlikely given the 14-2 vote count. The fact that the agency held this advisory meeting in the first place and invited Dr. Steven Nissen to present suggests to us that it is very willing to revise its requirements in this regard.
- **We believe that the most likely outcome will be a hybrid pre-approval screening study/ confirmatory trial requirement**. This could delay the approval of drugs slightly or significantly as the screening study would likely take at least two years or more to complete. Panelists indicated that two or three years would likely be the minimum amount of time required to see a clear cardiovascular safety signal. This hybrid trial system could be designed as a five year (or so) study beginning pre-approval and ending post-approval, with an interim analysis at two years, scheduled to occur at the time that the drug is filed. Alternatively, this hybrid system could consist of a shorter pre-approval trial, followed by a separate larger post-approval trial for any drug trending non-significantly in the wrong direction in the pre-approval trial. We expect the trials to run somewhere from 2,500 patients to 5,000 patients with a duration of two to five years. Approved drugs will likely have to undergo a post-marketing study of similar scale.
- **On the surface, the proposal for a cardiovascular safety study requirement is negative for all companies in the diabetes space, but different companies may be impacted very unequally.** The clinical trials could demonstrate cardiovascular benefit forsome classes of drugs, greatly expanding their use as other drugs fail to show such benefit in FDA- mandated clinical trials. Specifically, there is reason to believe that GLP-1s will be shown to bestow a cardiovascular benefit, and this could greatly expand the GLP-1 class. We think that Amylin and Novo Nordisk should be thinking about designing a PROactive-like study for Byetta and liraglutide, regardless of the FDA's final decision. The SGLT-2s could also prove to have cardiovascular benefits, given their similar association with weight loss. The requirement for a cardiovascular safety study would likely modestly or significantly delay the development of drugs that are currently in earlier stages of development. We believe that it is likely that drugs in phase 3 may instead be required to conduct a post-approval cardiovascular outcomes study.

-- by Mark Yarchoan and Kelly Close