Evaluate Vantage

November 06, 2007

CETP inhibitors – survivors proceed with caution

Lisa Urquhart

Once thought of as a multi-billion dollar holy grail of the pharmaceutical industry, CETP inhibitors are now more synonymous with being one of the graveyards of research.

The space, at one time thought be worth tens of billions of dollars, is littered with the corpses of numerous drugs, many of which have failed to make it beyond phase II of clinical trials.

This week Pfizer unveiled some of the findings of the post mortem it has been conducting for torcetrapib, its own CETP inhibitor whose failure shocked the industry and the market in December of last year.

The drug was scrapped after a phase III clinical trial demonstrated that patients using it in combination with the statin Lipitor had an almost 60% higher risk of death and a 25% higher risk of heart attack, than those on Lipitor alone.

Past failures

But put in context perhaps the failure of torcetrapib was not that surprising, given the number of other CETP inhibitors that have never made it out of clinical trials, yet alone to market. Since 2000 a total of five CETP inhibitors have failed to even make the difficult transition to phase III.

Bayer has notched up three of the failures, including its phase II product BAY-605521 that was dropped in June 2007. During 2002, Pfizer's CP-532,623 quietly slipped off the radar. Pfizer also still has two phase I CETP inhibitors that are now seemingly permanent parked on the laboratory bench.

The ongoing problems with CETP inhibitors, whose aim is to raise HDLs, or good cholesterol, have led some to start questioning whether there is a problem with the whole class of drugs, especially given that it is still not understood if all HDLs are good and where some of them can compromise the immune system.

But while others are mulling throwing the baby out with the bath water, the remaining two challengers in the field: Merck & Co with its anacetrapib and Roche with R1658, are taking heart from some of the findings. They might be able to avoid the pitfalls that scuppered Pfizer.

The dangers of aldosterone

So far the investigation into torcetrapib has found that while the drug achieved its aims of raising HDL levels, it also raised aldosterone levels in some patients - one of the widely talked about "off-target effects" of torcetrapib.

Aldosterone has been linked to higher incidence of heart attack. It was also found that alongside elevated aldosterone levels torcetrapib raised sodium level and lowered potassium levels, leading to an increase in blood pressure.

Merck has been one of the first to seize on the concerns about higher blood pressure associated with the Pfizer drug and in October published phase IIb data trumpeting the fact that its drug did not increase blood pressure levels.

The group has also conducted animal studies looking at aldosterone levels and setting its drug against torcetrapib. Aldosterone and blood pressure levels have only risen in rats given the abandoned Pfizer product, suggesting that the problems around torcetrapib could relate to that specific compound and not the entire family of drugs.

Accentuating the positive

Roche has also recently started to point to what it sees as clear blue water between R1658 and torcetrapib.

A spokesperson for the firm said: "Our drug has a unique chemical structure that is different to that used by

torcetrapib and to date our CEPT inhibitor has been well tolerated.”

But even with no problems reported yet, Roche, like Merck, is being vague about when they will move their product into phase III. The Swiss company, which is now working closely with health officials, said that it would have news about the product by the end of the year.

One thing is certain, both groups will be proceeding cautiously and will be closely watching any further data out of the studies into the failure of torcetrapib, leading many to believe that it still could be five years before there is a credible and safe CETP inhibitor on the market.