Abbott should benefit from direction of cholesterol debate

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Arbiter 6-Halts, a study that pitted Abbott Laboratories’ Niaspan against Merck & Co’s Zetia, has attracted a lot of attention for such a small trial, the reasons being it has touched on two huge areas of debate in the cardiovascular field.

Firstly it is down to the presence of Zetia, a component of Merck’s Vytorin which is already the subject of much controversy; observers from both the medical and financial worlds are keen to scrutinise any incremental evidence to determine whether current concerns about its efficacy are warranted. Secondly, the study speaks to a broader debate about the relative benefits of boosting “good” and lowering “bad” cholesterol levels. Despite important limitations this trial seems to add support to the former approach, no doubt to the satisfaction of Abbott, which has spent a lot of money in the last few years adding therapies that do just this.

Important limitations

The Arbiter 6 study set out to examine whether Niaspan or Zetia, on top of statin therapy, is better at unclogging arteries, a so-called surrogate endpoint assumed to indicate a lowered risk of a cardiovascular event (Event - Merck and Abbott shape up for cholesterol tussle, November 11, 2009). Both drugs are used when a patient’s cholesterol level is not adequately managed by statins alone, but work in different ways: Zetia helps to lower LDL levels even further, whilst Niaspan boosts HDL, or good cholesterol.

The Arbiter trial was stopped early, it has now emerged, because whilst Niaspan was busy ferrying away plaque, Zetia had no effect. A greater number of major adverse cardiac events were also detected in the Zetia group.

The fact that full results were only available from 208 patients means that the results from this study are far from conclusive. This was underlined by two editorials published in the New England Journal of Medicine, both of which describe the Arbiter-6 trial as intriguing, but at the same time stress it should be put into perspective.

They point out that the quality of the surrogate marker, carotid intima-media thickness, the statistical approach and in particular the consequences of terminating the trial early should all be taken into account.

One comments that because niacin is known to lower LDL levels as well as raise HDL, the study did not conclusively show that increasing HDL levels is more beneficial than augmenting the decrease in LDL, which should already be heading downwards due to first-line statin therapy. Previous studies of therapies that raise HDL failed to show clinical benefit, and in some cases were harmful. This is a reference to the failed Pfizer drug torcetrapib, which was abandoned in late 2006 after a large phase III study called Illuminate found more deaths among patients given the HDL-boosting CETP inhibitor.

Supporting the conclusion

Still, despite the caveats both editorials are largely supportive of the trial’s conclusion. One writes that despite the limitations the primary results are likely to be correct although the magnitude of the difference between the treatment arms may be overestimated.

Authors of the other editorial say that the results provide support for the concept that the use of statins to reduce LDL cholesterol with the subsequent addition of a drug to raise HDL cholesterol levels (niacin), rather than a drug to lower LDL cholesterol levels (ezetimibe), is a more effective treatment for patients at high cardiovascular risk.

Abbott is no doubt delighted with this outcome; the company has been pushing its cardiovascular franchise in this direction, of lipid management and HDL boosting in particular, for a number of years. Commencing with the long running partnership with Solvay over its fenofibrate franchise, which Abbott marketed in the US, followed by its $3.7bn acquisition of Kos Pharmaceuticals in 2006, which bought Niaspan into the fold, it culminated in the buyout of the Solvay unit two months ago, for $6.6bn.

The group has also pursued a partnership with AstraZeneca, whereby the two companies market each other’s flagship cholesterol drugs – namely TriLipix and Crestor – with a combination of the two, Certriad, currently filed with the FDA for approval.

Growing appreciation of the therapeutic benefit of boosting HDL levels can only help validate Abbott’s strategy with its cardiovascular franchise. Clearly, much more data is still required, particularly from large outcome studies, several of which
are underway.

In particular, there is a study that recruited 3,300 patients, run by the National Heart, Lung and Blood Institute, which is examining whether raising "good cholesterol" with a drug based on the vitamin niacin, while lowering "bad cholesterol" with a statin drug, can prevent more heart disease than the statin alone. The results will be due in 2011. Another study being run by the UK’s Oxford University, aided by Merck, is looking at niacin, statins and/or Zetia, with results due in 2013, whilst of course the big Vytorin outcome study, Improve-IT, due in 2012, is also keenly awaited.

Results in the coming months from other investigational therapies designed to manage lipids will also add to the debate. In particular, Roche’s CETP inhibitor R1658 and an Lp-PLA2 inhibitor from GlaxoSmithKline and Human Geneome Sciences are attracting attention.

If they all come to the same conclusions about HDL, Abbott will have positioned itself well to benefit.