Down to the wire in the PCSK9 class

The queue-jumping manoeuvre executed yesterday by Sanofi and Regeneron Pharmaceuticals to accelerate FDA review of alirocumab shows how tight the race is to launch the first in a new class of lipid-lowering drugs.

With Amgen preparing to file evolocumab in the third quarter it looks like two of these PCSK9 antibodies could be available by the end of 2015, at least for those with genetic mutations that lead to harmful cholesterol levels. The true promise of this class will not become clear until longer-term studies can generate mortality data indicating whether they can prevent cardiovascular deaths in the broad population of statin-resistant patients; even so, analysts are forecasting blockbuster numbers for the two leaders (see table).

Why wait?

Duelling announcements from Amgen and Sanofi/Regeneron this week demonstrated the intensity of the rivalry. A day after Amgen, in its quarterly earnings call, said it would file evolocumab for approval by the end of the third quarter, the alirocumab partners released results from the pivotal Odyssey programme.

But hours later Sanofi and Regeneron took an additional step, surprising the sector with the announcement that they had jointly purchased a priority review voucher from BioMarin, effectively slicing four months from first-pass review time (Putting a value on US priority review vouchers, July 31, 2014).

Given that Amgen had largely wrapped up the studies needed for an initial filing of evolocumab by the end of January, the purchase of early-boarding privileges was a competitive coup on the part of the alirocumab partners.

<table>
<thead>
<tr>
<th>The PCSK9 outlook</th>
<th>Sales ($m)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product</strong></td>
<td><strong>Company</strong></td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Amgen/Astellas</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>Sanofi/Regeneron</td>
</tr>
<tr>
<td>Bococizumab</td>
<td>Pfizer</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EvaluatePharma’s consensus forecast points to greater sales for Amgen’s candidate, suggesting the advantage of a steeper launch trajectory for a first-mover. This should be subject to change in coming months once analysts have greater clarity on filing and PDUFA dates, but it would not be at all surprising to see alirocumab’s forecast rise. One could just as easily see a scenario in which an FDA advisory committee is convened to vote its opinion on both at the same meeting early next year.

Odd man out is Pfizer’s bococizumab. Pfizer has been slow off the blocks in developing a subcutaneous formulation; an intravenous form of these drugs would almost certainly be a commercial flop because it would require physician administration.

Bococizumab has a healthy $563m forecast in 2020 nonetheless; Pfizer’s experience in selling drugs proven to lower the unhealthy low-density lipoprotein cholesterol (LDL-C) ought to give it some commercial advantage.

Eli Lilly is a late entrant to the game with LY3015014SC, as is Roche, which has more or less thrown in the towel on RG7652 and offered it up for licensing out. Sales forecasts are not available for either product.

Show me

The true potential for this class might not be realised for some time as the first approvals will probably only be
in patients with familial hypercholesterolaemia. The antibodies block PCSK9 – proprotein convertase subtilisin-like kexin type 9 – an enzyme that otherwise binds with LDL-C receptors primarily in the liver and inhibits metabolism of the so-called “bad” cholesterol. Statins are known to stimulate PCSK9, and thus blunt their cholesterol-lowering benefit.

The evidence of PCSK9s’ LDL-lowering potency is strong, and they have shown additive benefit to statins, which is why the early focus has been on familial hypercholesterolaemia; this is a defined population with known resistance to statins. The larger question is whether the bigger population of non-genetic patients unable to achieve LDL control on statins, or intolerant of statins, ought to be prescribed PCSK9s (AHA vantage point – Taking stock in PCSK9 class following new cholesterol guidelines, November 21, 2013).

Both the cardiology community and regulators want to see evidence of a mortality benefit, an obvious demand given that as biologicals the PCSK9s will be expensive drugs. A label expansion to the broader population would be a huge jackpot, as cardiologists estimate that 30-40% of patients could be candidates for the new therapies.

The 50,000-patient target for total enrolment in cardiovascular outcomes trials is a sign of what the eventual hope is for PCSK9s. This is easily a billion-dollar expenditure by the four companies combined, an investment they cannot hope to get back unless there is wider takeup of this promising category.

To contact the writer of this story email Jonathan Gardner in London at jonathang@epvantage.com or follow @JonEPVantage on Twitter