Evaluate Vantage

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ACC – Repatha’s next challenge is expectations

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Whether Repatha’s charmed life will be prolonged will be revealed as the curtain rises on the American College of Cardiology meeting next week, with specialists eager to see the magnitude of outcomes benefits with Amgen’s cholesterol-lowering injection.

The meeting will be a showdown of sorts between recently introduced and next-generation lipid-busters, as the Medicines Company will feature nine-month follow-up data from its phase II trial of the RNA-modulating project inclisiran (see table below). Both will have much to prove, as payers are eager to see whether a profound reduction of LDL can translate into prevention of cardiovascular complications and death, thereby justifying the drugs’ high price tags.

Appetites whetted

Amgen has already let some news slip on the Fourier trial, reporting a positive outcome, which suggests that when taken with a statin Repatha showed a relative reduction of 15% or more in the secondary endpoint, a composite of cardiovascular death, myocardial infarction or stroke, versus statins alone (*Fourier love all around as Repatha improves outcomes, February 3, 2017*).

Following the time-honoured tradition of saving full data for the key audience of medical specialists, Amgen has left the sector wondering how many deaths, heart attacks and strokes can be averted by using Repatha. This will be revealed at the meeting's opening session on March 17. At least one expert has challenged the 15% threshold, saying that based on the LDL lowering of 64%, Amgen could expect around a 30% reduction in cardiovascular events and deaths.

A cardiologist consultant to Mizuho Securities said the bare minimum of a 15% reduction in events and deaths would be bad for Amgen because the less expensive pill Zetia was able to reduce myocardial infarctions and strokes by a similar magnitude when added to statins.

The Mizuho consultant said a 20% reduction in cardiovascular events or death was a minimum to be considered meaningful for specialists, yielding an absolute risk reduction of one percentage point and requiring treatment of 100 patients to avert a single event. At that level, the consultant said he would want to see a price drop, however.

At greater reductions he would seek to expand the number of patients he puts on Repatha and its rival PCSK9 inhibitor Praluent. The consultant currently has just 50 patients on a PCSK9 drug, but he has 450 who are either intolerant of statins or have uncontrolled LDL on a maximum tolerated statin dose.

Moreover, payers will be closely watching data on the primary endpoint, which includes cardiovascular hospitalisations and revascularisations. Because patients commonly change insurers in the US, payers will want to see shorter-term benefit in the form of reduced hospital bills, and the primary endpoint has the potential to show that.

A broad view of payer and patient attitudes towards Repatha and Praluent could be provided on March 19 in another late-breaking presentation, which promises to reveal trends in insurance rejections and patients failing to fill prescriptions.

Seeking dosing advantage

Meanwhile, all will be watching the next candidate in LDL-lowering, the Medicines Company and Alnylam Pharmaceuticals’ inclisiran. This RNAi project has shown durable benefit in reducing cholesterol levels, with the two sponsors hoping to achieve the same efficacy as Repatha or Praluent on as few as two injections a year.

At the American Heart Association meeting last year the Medicines Company disclosed data from six-month follow-up of the Orion-1 trial, which revealed a patient death and a single case of liver enzyme elevations (*AHA – Medicines Company’s should-have-been day falls flat, November 16, 2016*). ACC will feature follow-up of up to nine months with a single or two doses of inclisiran, and thanks to the AHA presentation specialists and investors will be looking for additional safety signals as well as LDL-lowering durability.

ACC is not, of course, all about cholesterol lowering. The anti-diabetic SGLT-2 drugs have earned a prominent place in a late-breaking presentation detailing real-world data from the CVD-Real study on hospitalisations for heart failure, comparing SGLT-2s against other glucose-lowering agents.

On March 17 Medtronic is expected to present data proving that the latest iteration of its transcatheter aortic valve CoreValve matches surgical replacement in intermediate risk patients, likely enabling a label expansion into this large population. The snag is the perennial one Medtronic has faced in this space: Edwards got there first.

And on March 18 Bayer's Xarelto is pitted against aspirin in a pair of trials to be revealed as late-breakers. The factor Xa inhibitor will hope to outperform aspirin in extended treatment in one of its key indications, venous thromboembolism. Meanwhile, a comparison of bleeding events with low-dose Xarelto and aspirin in patients with acute coronary syndromes on PY12 inhibitors will help physicians evaluate the safety of Bayer's biggest-selling agent.

Major ACC 2017 presentations

Trial	Intervention	Setting	Abstract
Fourier	Repatha	Outcomes trial in high-risk patients on statin therapy	400-14
Orion-1	Inclisiran	High-risk patients on statin therapy	401-18
Surtavi	Corevalve	Vs surgical aortic valve replacement in intermediate surgical-risk patients	400-18
CVD-Real	SGLT-2 inhibitors	Vs glucose-lowering drugs in heart failure	415-14
	Xarelto	Vs asprin for extended treatment of venous thromboembolism	404-08
	Xarelto	Evaluation of bleeding events vs aspirin in acute coronary syndromes	404-10

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