Scrip
Pharma intelligence

# Can Cholesterol Drug Sponsors Make The Case For Statin Intolerance?

By Emily Hayes

**AMGEN'S FOURIER OUTCOMES STUDY OF REPATHA** supports LDL-lowering in high risk patients, but price may have to come down dramatically to spur wide use of the PCSK9 inhibitors with the subjective condition of statin intolerance.

• • •

The possibility of treating patients who cannot tolerate statins has long been eyed as a valuable segment of the cholesterol market, but has been a difficult claim to get past regulators. However, recent developments arguably may help build a market for what has been a hard-to-define population.

The majority of the cholesterol market is well-served by statins, which offer effective LDL lowering now as oral generic drugs. There are still patients who can't tolerate the side effects common to the class – including muscle pain and cognitive impairment. Off-label use in such patients helped drive **Merck & Co. Inc.**'s *Zetia* (ezetimibe) to blockbuster status.

Gaining an FDA approval for the indication has proven difficult, so later entrants to the cholesterol field have focused on high-risk subpopulations and those with rare genetic forms of hypercholesterolemia. But there are still hopes that with better evidence of effect on cardiovascular outcomes, those products may get broader use, including in the statin intolerant segment.

**Amgen Inc.** and **Sanofi/Regeneron Pharmaceuticals Inc.** had originally hoped to gain statin intolerant claims for their PCSK9 inhibitors *Repatha* (evolocumab) and *Praluent* (alirocumab), respectively, but hit a roadblock at the US FDA. New outcomes data support treatment to low LDL levels and could spur broader use, plus labeling allows for use in patients on "maximally tolerated statins" – which could mean none.

Recently, **Esperion Therapeutics Inc.** announced it had worked out a plan with US regulators to gain a statin intolerant indication for its bempedoic acid, an oral inhibitor of ATP citrate lyase, by conducting a cardiovascular outcomes trial (CVOT) in that population.

Amgen presented the first CVOT for the PCSK9 class at the American College of Cardiology annual meeting in March. Although Amgen's FOURIER trial was in patients taking statins, the cardiovascular outcomes benefit arguably gives a leg up to the PCSK9 inhibitor class for treatment of statin intolerant patients – though pricing may still have to come down dramatically to spur wide use in this population.

The release of Amgen's FOURIER outcomes study of Repatha in a patient population at high risk for events and well managed on statins has renewed debate about wider use of the drugs, including treating statin intolerant patients.

## Defining Statin Intolerance

Datamonitor Healthcare estimates that there were 264m cases of hypercholesterolemia in adults in the US, Japan and five major EU markets in 2015. Overall, 34.4% of these cases are associated with high risk for coronary artery disease. Statin intolerance for a variety of reasons continues to represent an area of unmet need, despite many approved treatments in a highly genericized market, and a lucrative segment.

According to Datamonitor's proprietary survey of prescribers in November 2016, rates of statin intolerance ranged from 9% to 17% in the US, Japan and five major EU markets (*see table*).

But statin intolerance has always been a subjective term, prone to controversy. Amgen and Sanofi originally sought to get claims for treating statin intolerant patients included in labeling of their PCSK9 inhibitors. But instead, they both got similar labeling for use in particular populations – on top of maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia and for use in patients with clinical atherosclerotic cardiovascular disease who need additional LDL lowering *(Also see "Praluent Sponsors Set Tone For PCSK9 Labeling, Post-Marketing Negotiations" - Pink Sheet, 18 Jan, 2016.)*. Repatha is also cleared for an additional indication for use with other LDL lowering therapies in treating the rare genetic disease homozygous familial hypercholesterolemia.

At the time of approval in 2015, the sponsors maintained that this labeling for "maximally tolerated" statins in effect includes statin intolerant patients *(Also see "Broad Enough? Sponsors Pleased With Narrower Praluent Label" - Pink Sheet, 24 Jul, 2015.)*.

## Statin Intolerance Rates For Secondary Prevention, Major Markets

| Region | Pure Hypercholesterolemia (elevated LDL) | Mixed Hyperlipidemia (elevated LDL and elevated triglycerides) |
|---|---|---|
| All | 13.3% | 13.9% |
| US | 14.2% | 13.5% |
| UK | 14.8% | 15% |
| France | 16.6% | 16.6% |
| Spain | 9.1% | 9.9% |
| Germany | 11% | 12.5% |
| Italy | 16% | 16.2% |
| Japan | 11.4% | 13.4% |

*Source: Datamonitor Healthcare's proprietary dyslipidemia survey, November 2016*

Statin intolerance has been a challenging issue to deal with in the FDA review process. In the review documents for the PCSK9 inhibitors, FDA said that its working definition of statin intolerance was a patient who is not able to tolerate the lowest starting daily dose of a statin, in addition to any dose of another statin, due to symptoms that began or increased during statin therapy and ended when statin therapy stopped.

The agency questioned whether the PCSK9 sponsors were using adequate criteria for statin intolerance in their trials; FDA noted that in Sanofi/Regeneron's ALTERNATIVE trial, experience with a statin validation arm the sponsors included showed that 70% of patients who were statin intolerant due to muscle symptoms, could actually withstand treatment with a statin (atorvastatin at 20 mg, **Pfizer Inc.**'s *Lipitor* and generics) in a validation arm of the study. The regulators argued this showed the value of rechallenging with a statin. *(Also see "Praluent Panel To Focus On Indication Breadth Absent CV Outcomes Data" - Pink Sheet, 5 Jun, 2015.)*

Since the PCSK9 inhibitor approvals, Amgen released a new Phase III study in statin intolerant patients that did include rechallenging with a statin. *(Also see "Amgen's Statin Intolerance Study May Not Cure What Ails PCSK9 Inhibitors" - Scrip, 4 Apr, 2016.)* In the GAUSS-3 trial, Repatha was associated with much greater LDL-lowering than Merck's Zetia. Reports of muscle pain were not that much lower than Zetia – 20.7% vs. 28.8% – but discontinuation rates associated with this adverse event were low at 0.7% and 7% for Repatha and Zetia respectively.

GAUSS-3 initially had two ten-week crossover periods, during which time the 491 patients in the study were randomized to atorvastatin or placebo, followed by a washout period and then, for those who could tolerate it, randomization to the alternate treatment. Cedars-Sinai's cardiologist Sanjay Kaul points out that the results show the challenges of making a diagnosis of statin intolerance – only 43% of patients developed statin intolerance while taking atorvastatin but not placebo, 27% while taking placebo but not atorvastatin (perhaps related to the "nocebo" effect) and 17% while taking both treatments.

"So only 60% (43 + 17) developed statin intolerance to atorvastatin, even though a well-documented muscle-related adverse effect to two or more statins was an entry criterion. Interestingly, one-fifth of the statin intolerant patients in GAUSS-3 still reported muscle-related adverse effects while taking evolocumab," Kaul said.

While the agency was wary of including specific labeling for statin-intolerant labeling, FDA officials had also noted in review documents that "language that indicates use in combination with 'maximally tolerated statin therapy' would recognize that, for some patients, maximally tolerated statin therapy may be no statin therapy at all."

"I think the FDA was very smart and gave a lot of freedom there in terms of defining the disorder. It's a tough disorder to define scientifically," said Robert Eckel, director of the lipid clinic at University of Colorado Hospital.

Eckel expects that FDA will continue with this approach – that is, rather than using the term "statin intolerant" in labeling it will approve claims based on trial entry criteria.

## Will It Work For Esperion?

Coming late to the cholesterol market, Esperion has been steering development of its bempedoic acid heavily toward the statin-intolerant population. *(Also see "Esperion Says FDA Stance Means No Clear Regulatory Path For ETC-1002" - Scrip, 29 Jun, 2016.)*

Asked to comment on Esperion's plans in January 2016, FDA confirmed that its views on statin intolerance were in line with sentiments expressed during the reviews of the PCSK9 inhibitors. In an email to the *Pink Sheet* at that time, the agency reiterated its concerns about the risk of encouraging patients to prematurely abandon statins, though this could be mitigated if a drug were to demonstrate a favorable effect on CV morbidity/mortality in an outcomes trial that is applicable to a "statin-intolerant" population.

The agency declined to comment further, but Esperion recently said that FDA is on board with its plans to do an outcomes study specifically in statin-intolerant patients. The initial approval would be based on Phase III trials in high-risk patients, as with the PCSK9 inhibitors, but by doing the CVOT in statin-intolerant patients, an indication matching that trial population could later be added to labeling.

The CLEAR Outcomes study tests the drug in 12,600 patients who are statin intolerant, which the company says for the purposes of the trial is defined as "inability to tolerate two or more statins, one at the lowest approved daily starting dose, due to an adverse effect." Participants will have cardiovascular disease or be at risk for it.

Requiring two or more statins, including at the lowest dose, may get around some of FDA's earlier concerns about re-challenging patients, although unlike GAUSS-3 the re-challenge is not done as part of the controlled trial.

## Implications Of FOURIER

In Amgen's FOURIER trial, Repatha yielded a 15% reduction for the primary endpoint related to major adverse cardiovascular events and a 20% reduction in a secondary endpoint related to cardiovascular death, myocardial infarction or stroke.

The level of benefit may not have lived up to expectations and there was no decrease in mortality events, but follow-up lasted only two years and it is possible that the benefit in terms of death rates would have been shown over a longer period. *(Also see "Is Amgen's FOURIER Enough For Physicians, Payers To Expand Repatha Use?" - Scrip, 17 Mar, 2017.)*

The results from FOURIER may be interpreted as encouraging when it comes to treating the statin intolerant population, even though the CVOT was not in a statin-intolerant population. To get into the FOURIER study, patients needed to be on a maximally tolerated dose of statins and to be at high-risk for cardiovascular events. Consequently, 69% of the study population was on high-dose statins and the baseline LDL in the trial was 92 mg/dL.

The trial showed a reduction in events regardless of the starting LDL level. And the mechanism of action, already well accepted, was strengthened by the

outcomes trial results. Furthermore, some experts believe that a benefit for mortality might be seen if the study was longer.

Eckel commented that he is excited about the data and that the results support getting patients down to lower LDL levels. The last version of LDL treatment guidelines from the American College of Cardiology and American Heart Association, issued in 2013, moved away from treating to particular targets and toward a focus on risk. *(Also see "Cholesterol Guidelines Look High And Low: Statin Market Extended At Both Ends" - Pink Sheet, 13 Nov, 2013.)* The guidelines are now being revised and many specialists – including Eckel, who was involved in writing the 2013 version – believe it is possible there may be a move back toward endorsing targets.

To date, 70 mg/dL has been ingrained as an LDL target for patients at high risk of a cardiovascular event, but the FOURIER and IMPROVE-IT study of Merck's Zetia suggest an even lower target of at least 55 mg/dL may be appropriate, he said. *(Also see "PCSK9 Inhibitors May Feel Effects Of FDA Judgment On IMPROVE-IT" - Pink Sheet, 25 Jan, 2016.)*

A spokesperson for the AHA said that the process of reviewing results from relevant scientific research, including the results from FOURIER, has begun but that it is too early to predict when the guidelines will be completed or how they will change. Results from Sanofi/Regeneron's ODYSSEY outcomes study of Praluent are due later this year.

The authors of the last version of the guidelines took a cautious approach toward statin intolerance, advising prescribers to investigate whether there might be another cause for symptoms and whether patients were truly intolerant. Eckel is not expecting changes in the way statin intolerant patients are handled in the next version of guidelines.

What FOURIER means for the market of patients who are intolerant to statins remains to be seen. The class is certainly capable of much more dramatic LDL lowering than alternatives like Zetia and therefore represent a more robust option for statin intolerant patients.

However, the injectable PCSK9 inhibitors also cost a lot more, with a list price of about $14,500 per year. Amgen contends that its net price of Repatha, including discounts, is more in the range of $7,700 to $11,200 annually. The company sees the FOURIER results as supporting the current pricing. *(Also see "Amgen Says Repatha Outcomes Trial Backs Up Its Pricing Math" - Pink Sheet, 19 Mar, 2017.)* Sanofi declined to comment on the net price for Praluent, which has a similar list price.

## How Prescribers Will Respond

PCSK9 inhibitors have been tightly managed by insurance companies to date, which has had a negative impact on sales. But questions have remained about whether outcomes data would make a difference in prescribing patterns and reimbursement. Roger Longman, chief executive officer of the reimbursement intelligence company Real Endpoints, has noted that there are management costs associated with rejecting requests and that if demand rises enough, payers will respond.

Although FOURIER was not designed to assess outcomes in statin-intolerant patients, the improvement in clinical outcomes with the demonstrated LDL lowering should make patients and clinicians reasonably comfortable with the choice of a PCSK9 inhibitor as an alternative for LDL lowering when it is required and statins are not tolerated, commented Robert Harrington, chair of the department of medicine at Stanford University.

"I suspect that there will be an increase in treatment for this group although costs will be an issue, as will insurance coverage," he added.

The expectation is that through FOURIER, Repatha will get a cardiovascular risk reduction claim.

It's unclear whether the agency would note in the phrasing of the claim on labeling that the drug is to be given on top of high-intensity statins. Most, but not all of the patients in the study were on high-intensity statins; others were on lower doses. If labeling gives a broad claim for risk reduction on top of statin therapy, this could include patients who are able to take a low

dose of a statin and yet whom may still be regarded as statin intolerant.

"If the FDA allows a CV risk reduction claim for evolocumab based on FOURIER, I think the clinicians should be able to use the drug in patients deemed truly statin-intolerant, provided the payers allow it," Cedars-Sinai's Kaul commented.

Kaul expects that for a specific indication or claim in statin intolerant patients, the FDA would need to see outcomes data specifically in that population – like Esperion is planning – but said that it's unclear whether clinicians or payers really need an FDA-approved indication for statin intolerance.

PCSK9 inhibitors are more effective than Zetia for getting patients to target, so PCSK9 inhibitors should be preferred.

"In my opinion, the cost would need to be discounted heavily for me to consider PCSK9 inhibitors ahead of ezetimibe in this patient population. Based on the FOURIER results, the 1.5% absolute risk reduction in both the primary and the key secondary endpoint translates into a NNT [number needed to treat] of 66 over a median follow-up of 2.2 years. At an annual cost of $14,500, this means that the cost of preventing 1 event is over $2 million. Even at a 50% discount, the $1 million cost of preventing one event does not offer a value proposition," Kaul commented.

Even if the FDA approved a specific indication in statin intolerant patients (a best-case scenario), the prohibitive cost and the skepticism of payers would still pose a barrier against widespread use, Kaul added.

Given the estimated number needed to treat to prevent an event, in Kaul's view, it's hard to make the case that PCSK9 inhibitors provide value without a major discount – at least 75%.

Eckel also felt that reimbursement is hugely important in terms of using PCSK9 inhibitors in statin intolerant patients. Typically, insurers want to see that the condition has been documented and that patients have tried two different statins for six weeks. Often they will also require that a patient has tried Zetia. They may also want to see results from a creatine phosphokinase (CPK) test if the issue is muscle pain, but these tests are often normal, muscle pain being subjective, Eckel commented.

"It's really an art of medicine, not a science," he said.

Payers are really looking for proof in certain populations and have difficulty with the idea of statin intolerance, commented Edmond Pezalla, an independent reimbursement consultant in Hartford, Conn. and former policy and strategy executive at **Aetna Inc.** And FOURIER was done in combination with statins, not as an alternative to statins, so it is questionable whether they would make the leap to assuming the results would apply to patients with statin intolerance, especially considering the cost of the drugs, he said.

Pezalla said that it is terrific that FOURIER showed that getting patients down to as low as 30 mg/dL still improved outcomes, but the only way to get the drug to a broader population is to bring the price down.

A net price closer to $4,000 per year would boost uptake, he suggested.

The Institute for Clinical and Economic Review (ICER) announced March 17 plans to update its assessment of comparative clinical effectiveness of PCSK9 inhibitors, including a re-calculation of a value-based pricing benchmark, to take FOURIER data for evolocumab into account. The initial ICER assessment called for a 67% price reduction, which was later revised to 47% discount to the list price. *(Also see "PCSK9 Revised Analysis Indicates Less Price Discounting May Be Needed" - Pink Sheet, 9 Oct, 2015.)*

The ICER update, which is slated for mid-May, could have implications for payers' expectations.

*Published online April 20, 2017*