Scrip
Pharma intelligence

Is Amgen's FOURIER Enough For Physicians, Payers To Expand Repatha Use?

By Mary Jo Laffler

DETAILED RESULTS PRESENTED AT ACC SHOW a reduction in risk of major adverse cardiovascular events, but perhaps not at the level hoped for by payers.

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As the significance of the level of benefit seen in **Amgen Inc.**'s FOURIER cardiovascular outcomes trial is debated, the company announced a new rebate program to encourage and support use of its PCSK9 inhibitor *Repatha* (evolocumab).

Amgen had already announced the overall positive results of FOURIER in February, but the details were not known until its presentation at the American College of Cardiology (ACC) annual meeting on March 17 in Washington, D.C.

And while the data will likely be embraced by practitioners – who have been hesitant to use Repatha and **Sanofi/Regeneron Pharmaceuticals Inc.**'s competing *Praluent* (alirocumab), both of which are injectables that cost around $14,000 per year – it may not be enough to sway payers. However, Amgen appears to be trying to get ahead of any pushback.

"To underscore the company's conviction around these outcomes results, Amgen will offer additional contracting options in the US to payers willing to remove access barriers. These options include one that offers a refund of the cost of Repatha for all of their eligible patients who have a heart attack or stroke. In addition, Amgen will continue to offer innovative contracts that provide reasonable budget predictability to help address budget impact concerns raised by payers," the firm announced in conjunction with the FOURIER results.

The specifics will be negotiated with each payer, but "for any compliant Repatha patient who had a heart attack or stroke after taking Repatha for at least six months, payers would receive a refund in the form of an additional rebate" for what they spent on Repatha, Amgen told *Scrip*.

"These robust data, from one of the largest outcomes trials ever conducted, validate that the net prices of Repatha in the market today are value-based. Now that Repatha has proven a meaningful reduction in cardiovascular events, we expect payers to remove onerous barriers and help appropriate patients get access to Repatha," Joshua Ofman, senior vice president of global value, access and policy, said in a statement. "We look forward to working with payers to improve the health of their patients at high risk of heart attacks and strokes and discussing innovative contracting options over the coming months."

Amgen already offered patient and provider support through its *RepathaReady* program, including copay assistance and insurance coverage support, as well as patient assistance for qualifying patients with no or limited coverage through the Amgen Safety Net Foundation.

The company thinks that the FOURIER data are enough to prompt payers to change their stringent usage criteria, which have held up utilization and sales of the drug. *(Also see "PCSK9 Inhibitors' First Birthday Brings Sluggish Sales And More Bad Press" - Scrip, 16 Aug, 2016.)*

Payer Reactions

When it comes down to it, FOURIER "showed benefit in the right direction," **Express Scripts Holding Co.** Chief

Medical Officer Steve Miller told *Scrip*. "Maybe not the benefit some were hoping for, but it was incrementally better. The question is whether it is incremental enough to justify $14,000 a year." Repatha's current annual wholesale acquisition cost is $14,523, though the net price ranges between $7,700 and $11,200 per year.

Miller thought that the outcomes data would spur demand and that doctors "will be a bit more enthusiastic." With just LDL data and no evidence of the consequence, the drugs were not met with a lot of enthusiasm, but now with the outcomes data he thinks payers "will be appropriately more willing to pay."

He noted that Express Scripts has been working on several ideas with both Amgen and Sanofi, and has worked with the FH Foundation about streamlining access to the PCSK9 inhibitors for patients with familial hypercholesterolemia (FH). Express Scripts is "actively" working on a program with Amgen.

The risk reductions in FOURIER fell short of what Real Endpoints CEO Roger Longman had predicted were necessary to change payer policies. *(Also see "What To Look Out For At ACC" - Scrip, 13 Mar, 2017.)* "I don't think payers are going to do much in the next year or so to change their coverage policies," which have restrictive prior authorization requirements but do "nominally" cover the drugs, he said.

"It's less about how payers will respond to the data and more about how physicians are going to respond to it," Longman explained. And, if there's enough demand from prescribers, the management costs of rejecting requests start to add up and "that could change coverage."

Longman suggested that more change could come when subgroup data are analyzed, to see what the benefit is in the patients with even higher risk factors, such as a recent heart attack or diabetes and atherosclerotic cardiovascular disease (ASCVD). "If I were a payer, I might be willing to do deals in these extreme risk patients – these guys might get faster coverage, easier coverage, and the regular high risk patients might still be covered with these somewhat challenging restrictions," he said.

The number of patients that need to be treated to prevent an event is also a critical figure for payer calculations. In FOURIER, 74 patients needed to be treated for at least two years to prevent a cardiovascular (CV) death, heart attack or stroke. In another calculation in an appendix to the *New England Journal of Medicine* (NEJM) publication of the results, lead investigator Marc Sabatine, Harvard Medical School, noted that the number needed to treat to prevent one element of the composite endpoint over five years as used in a major meta-analysis of statin results (CTTC) was 17, "calculated by taking the annualized incident rate for the CTTC composite endpoint in the placebo arm (5.34%), multiplying that rate by 5, and applying the relative risk reduction (22%) in the CTTC endpoint after the first year (analogous to the CTTC approach to quantifying long-term benefit), which yields an absolute risk reduction of 5.9%, or a number needed to treat of 17."

"That's the kind of math that payers will need to be doing," Longman said. "Is the price of the drug, the offset here really worth it? It may be."

During a same-day investor briefing from ACC, Amgen executives noted that utilization management criteria have already been changing, and that the firm has "numerous" risk-sharing agreements in play for Repatha. Amgen execs also argued during the firm's investor briefing that number-needed-to-treat is not the best metric for health economic research.

Key Findings

Amgen's drug reduced the risk of the primary endpoint of cardiovascular death, myocardial infarction (MI), stroke, hospitalization for unstable angina or coronary revascularization by 15%, and there was a 20% reduction on the harder secondary endpoint of CV death, MI or stroke. There was also a 59% reduction in LDL from baseline, which "was sustained without evidence of attenuation," according to a *New England Journal of Medicine* (NEJM) publication of the results concurrent with the ACC presentation on March 17 (*see box*).

FOURIER DETAILS

- Double-blind, placebo-controlled trial in 27,546 patients with atherosclerotic CV disease and LDL levels of 70 mg/dL or higher while receiving statin therapy; patients were randomized to evolocumab 140 mg/2 weeks or 420 mg/month or placebo
- Primary endpoint was composite of CV death, myocardial infarction (MI), stroke, hospitalization for unstable angina or coronary revascularization; key secondary endpoint was composite of CV death, MI or stroke
- Median duration of follow-up was 2.2 years
- Median LDL was 92 mg/dL; 69% of patients were on high-intensity statins, 30% on moderate statins, 5% on ezetimibe
- At 48 weeks, mean reduction in LDL of 59% for evolocumab compared to placebo, to 30 mg/dL. A quarter of the patients had LDL less than 20 mg/dL.
- For primary endpoint, evolocumab had a 9.8% rate of MACE vs. 11.3% for placebo (HR 0.85); on the key secondary endpoint evolocumab had a 5.9% rate of expanded MACE vs. 7.4% for placebo (HR 0.80)

However, many analysts were expecting at least a 20% reduction on the primary endpoint and Evercore ISI analyst Umer Raffat further noted that his survey of investors showed that 70% had been expecting to see a mortality benefit, which was not demonstrated in the trial.

There was no effect overall on cardiovascular death, but Sabatine said in his ACC presentation of the FOURIER results that there were directional trends for death due to acute MI and death due to acute stroke, although they were infrequent. Evolocumab reduced the risk of MI or stroke by 21% to 27%. There was no difference for hospitalization for unstable angina.

"Over the past decade, none of the trials of intensive LDL lowering versus moderate statins showed a reduction in CV mortality," Sabatine pointed out, noting that with contemporary medicine, CV death "is less common than it was in the past." The rate of CV mortality in FOURIER was one-third the rates in the landmark Scandinavian Simvastatin Survival Study (4S), the NEJM study adds.

The investigators similarly ascribed the lack of effect on unstable angina to the increased specificity of the assays used today, suggesting that probably most hospitalization for chest pain without biochemical evidence is likely not truly cardiac ischemia.

The study reinforces that long-term treatment matters, and longer follow up could reveal greater levels of benefit. "The magnitude of risk reduction with regard to the key secondary endpoint appeared to grow over time, from 16% during the first year to 25% beyond 12 months, which suggests that the translation of reductions in LDL cholesterol levels into cardiovascular clinical benefit requires time," Sabatine and his co-authors wrote.

Beyond the first year of treatment, evolocumab showed a 35% reduction in heart attack and a 24% reduction in stroke, Sabatine told Amgen's investors.

Datamonitor Healthcare analyst Jack Allen commented that the risk reduction at five years, as has been shown in many statin trials, might show further benefit for evolocumab and should lower the number needed to treat to prevent an event.

Reassuring Results

The long-term results from the outcomes trials were also critical confirmation of the PCSK9 inhibitor's safety and of the value of treating to low LDL levels.

FOURIER demonstrated a clean safety picture across the board, including no signal in adverse events that had been areas of concern – like neurocognition and diabetes.

"Prolonged exposure to extremely low LDL cholesterol levels could negatively affect neurocognitive function

and might result in impaired cellular delivery of fat-soluble vitamins," Robin Dullaart, University of Groningen, explained in a NEJM editorial. "Reassuringly, alirocumab administration was not found to be associated with an increased risk of diabetes in a preliminary analysis."

There were no patients with neutralizing antibodies, which proved to be a major factor for **Pfizer Inc.**'s terminated PCSK9 inhibitor bococizumab.

Aside from the support for Repatha, FOURIER will stand as a "landmark" trial establishing the value of reducing LDL to very low levels – carrying on work done with high-intensity statins and combination therapy of statins plus ezetimibe (PROVE-IT-TIMI 22, TNT, IMPROVE-IT) down to levels as low as 54 mg/dL.

In the lowest quartile of LDL levels in FOURIER, evolocumab yielded a 22% reduction in the risk (extended MACE) with median LDL reduced from 73 mg/dL to 22 mg/dL. In the highest quartile, reduction in risk was 17% as median LDL went from 126 mg/dL to 43 mg/dL, which the investigators noted was equivalent to the lowest quartile in the ezetimibe-plus-statin study IMPROVE-IT.

The quartile findings "show that continued cardiovascular benefit can be accrued even when LDL cholesterol levels are reduced to 20 to 25 [mg/dL], a range that is well below current targets," the article states.

Physician Reactions

Physicians at ACC seemed most excited by the evidence that treating to very low LDL levels has significant benefit. During his presentation, Sabatine highlighted that "even lower LDL now appears to be even better."

The magnitude of benefit for evolocumab is "largely consistent with the benefit seen with statins on a per-millimole-per-liter basis of LDL cholesterol lowering," the NEJM article notes. Sabatine showed that the two-year results of FOURIER compared favorably to the year two results of five-year statin outcome trials, so the data now shows that LDL lowering is consistently beneficial across modalities and that there's greater benefit as levels get lower.

"All the data suggest that LDL is such an important risk factor," he said. "You want to get it down as low as you can go."

Sabatine expects additional benefit to be seen with further analysis. "Risk factor modification takes time, as has been well seen in the statin trials," he said.

Further analysis of the trial will give greater detail on the patients that are most appropriate for treatment. "Which patients are at highest risk is going to be the source of a lot of consideration, because of the price of the drugs," panelist David Cohen said – to which Sabatine only said, "Agreed."

Amgen notes that the response it has been getting from expert cardiologists is universally that it is game-changing data.

What Next?

Amgen is continuing a long-term extension cohort of 6,000 patients for longer follow-up, and additional subgroup analysis is also eagerly awaited.

"The efficacy, with regard to atherosclerotic cardiovascular disease, of PCSK9 inhibition treatment that is started shortly after an acute event still needs to be determined, as does the efficacy of the treatment in other categories of high-risk patients," Dullaart said in the NEJM editorial.

The FOURIER design matched the already labeled population, so expansion into new populations – notably the difficult target of "statin-intolerant" patients – will require additional studies.

"I'm not aware of any drug with this kind of result that was not added to the label, guidelines [and was] practice-changing," Elliott Levy, senior vice president of global research and development at Amgen, told *Scrip*. "It's hard to see how it wouldn't be."

As to guidelines, it's a matter of when. "It is anticipated that the results of the FOURIER trial will soon be implemented in international guidelines regarding the treatment of high-risk patients, directing clinicians in the use of this new and expensive class of drugs," Dullaart said.

STILL ROOM FOR INCLISIRAN

The Medicines Co./Alnylam Pharmaceuticals Inc. presented ORION-1, a Phase II dose-finding study on their siRNA inclisiran, a long-acting PCSK9 option. "RNAi offers an alternative approach by going directly to the source and inhibiting synthesis of PCSK9 in the liver," lead investigator Kausik Ray told ACC. Inclisiran produced a clear effect; all patients appeared to respond, with mean LDL down as much as 52.6% at six months. There were no safety issues, including liver function tests and myalgia, which have been concerns for lipid-lowering drugs.

The companies see a clear adherence benefit for their drug, which will be studied in Phase III with an initial dose, a dose at day 90 and then once every 180 days. In contrast, the anti-PCSK9 monoclonal antibodies require 12-36 injections a year. Both the PCSK9 inhibitors and statins have roughly 50% compliance, Ray said. That means LDL levels can be variable, which results in poorer outcomes. Inclisiran is moving into Phase III and a CVOT in high-risk primary and secondary prevention patients.

Evercore ISI's Raffat said in a March 17 note that The Medicines Co. thought it could improve on Amgen's CVOT design by excluding hemorrhagic stroke, using hard MACE as the primary endpoint, excluding arrhythmia-related CV deaths and using a longer duration of observation.

Datamonitor's Allen noted that inclisiran could have a cost advantage, which could make it a game changer.

Sabatine noted he expects guideline revisions within a year, although there is also the possibility that the guidelines committee will wait until Sanofi/Regeneron's ODYSSEY OUTCOMES trial is published in a peer-reviewed journal. Cleveland Clinic cardiologist Steve Nissen said in an interview that he expects the guidelines to recommend PCSK9 use in high-risk patients and suggest it be considered in medium-risk patients.

Amgen estimates there are 11 million people with ASCVD and/or familial hypercholesterolemia who have uncontrolled levels of LDL-C over 70 mg/dL despite treatment with statins or other cholesterol-lowering therapies.

Repatha brought in $141m in sales in 2016. The PCSK9 sponsors have attributed disappointing performance since launch to payers and physicians holding out for outcomes data – which will make 2017 the true test of how much that has been a limitation.

Lessons From Pfizer's Failure

In addition to the FOURIER results, the ACC meeting kicked off with the presentation of the SPIRE-1 and -2 trials of Pfizer's PCSK9 inhibitor bococizumab. The outcomes trials had been halted in late 2016, when Pfizer pulled the plug on development because of anti-drug antibodies detected across the clinical trials. *(Also see "Pfizer's Bococizumab Discontinuation Increases Uncertainty For Other PCSK9s" - Scrip, 1 Nov, 2016.)*

No significant benefit was seen in the pooled analysis or in SPIRE-1 in lower-risk patients. But in the higher-risk SPIRE-2 population with a longer duration of observation, bococizumab showed a significant benefit consistent with FOURIER, lead investigator Paul Ridker noted during his ACC presentation.

The full clinical program was analyzed with an eye toward better understanding the class, Ridker said. Bococizumab had a clear problem with neutralizing antibodies, and that was associated with an attenuation of the LDL lowering effect. However, even without the presence of antibodies, there was a wide variability in responses, which Ridker took as an indication that "on-treatment measurement of LDL will be important for clinical practice."

Dullaart also noted in the NEJM editorial that the mechanistic process by which PCSK9 acts "suggests that interindividual differences in plasma PCSK9 concentrations are pathophysiologically relevant."

Whether physicians and payers consider LDL monitoring necessary remains to be seen, but Real Endpoints' Longman noted that it would be very challenging and expensive for any payer to collect that type of lab data.

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