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Will Physician Demand For Repatha Put Pressure On Payer Restrictions?

19 Mar 2017 | **ANALYSIS**

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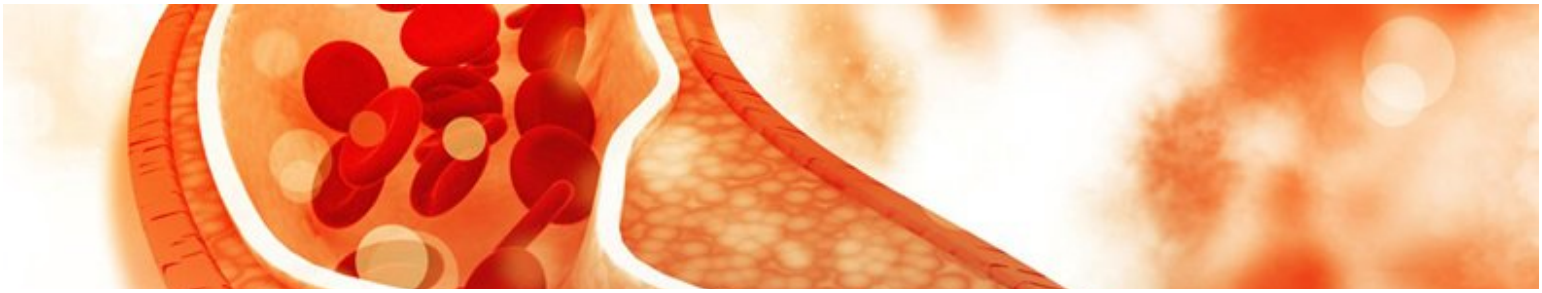
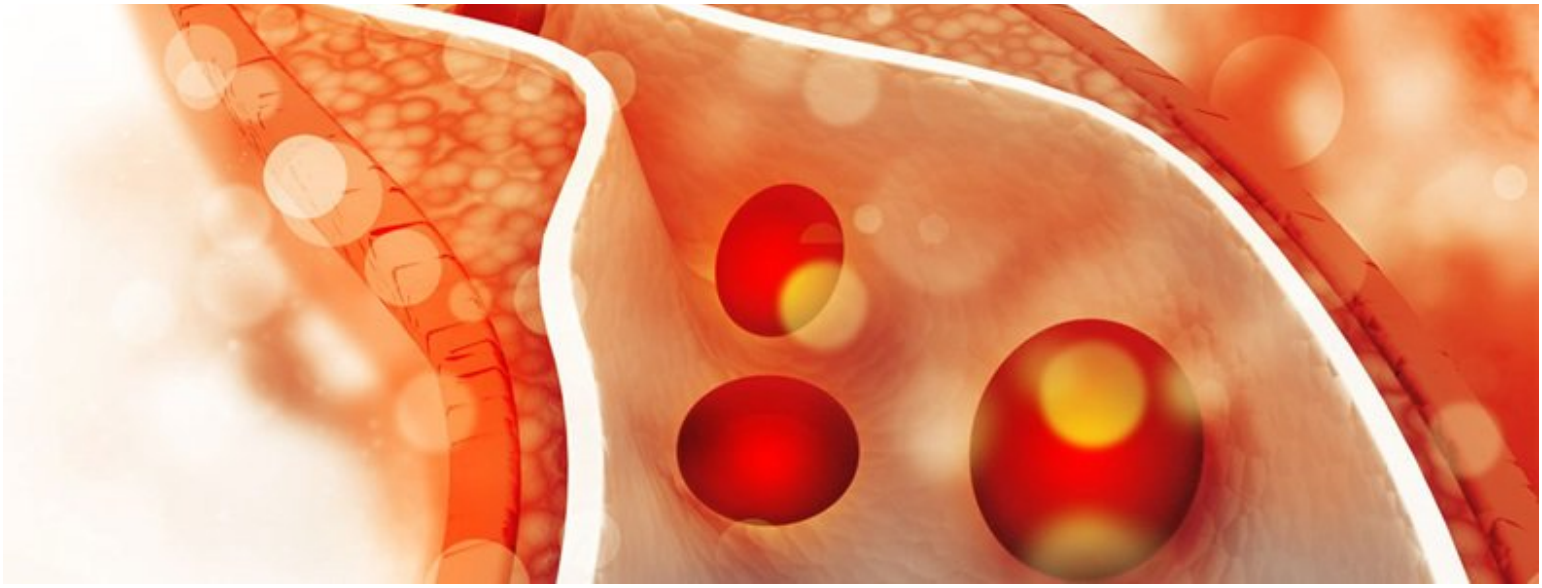
Executive Summary

FOURIER outcomes data presented at the American College of Cardiology annual meeting fell short of expectations, but could increase physician demand for the PCSK9 inhibitor, making it harder for payers to say no.





Physician demand could wind up being a determining factor in whether the reimbursement outlook for **Amgen Inc.**'s *Repatha* (evolocumab) improves following the long-awaited release of cardiovascular outcomes data for the PCSK9 inhibitor.

While the overall positive results of Amgen's FOURIER trial were announced last month, the level of benefit was unveiled March 17 at the American College of Cardiology annual meeting, in Washington, D.C. Repatha yielded a 15% reduction in a composite of major adverse cardiovascular events and no mortality benefit, short of expectations (*see box*).

But the benefit is being well received by practitioners and that might bring about enough increased demand to prompt payers to relax their utilization management criteria.

More important than how payers are responding to the data is "how physicians are going to respond to it," Real Endpoints CEO Roger Longman suggested in an interview. Payers do "nominally" cover Repatha and **Sanofi/Regeneron Pharmaceuticals Inc.**'s rival PCSK9 inhibitor *Praluent* (alirocumab) at the moment, albeit with "some challenging prior authorization requests," he noted.

"One of the big motivations for a payer to be a little more liberal in its interpretation of its own prior authorization criteria is the cost of saying 'no,'" Longman suggested. "From the payer point-of-view, the more it says no and the more times a physician appeals, the more the management cost is to the payer. If you have a lot of physicians prescribing and then appealing, that's a big cost. That could change coverage."

One study presented at ACC showed that 80% of Repatha and Praluent prescriptions are initially rejected, and more than half are never approved. Duke Clinical Research Institute's Ann Marie Navar, who presented

the analysis based on prescription data from Symphony Health Solutions, reported patients may have to go through five appeals – and even once approved, one-third of prescriptions are not filled largely due to copay costs.

> **"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," Amgen's Ofman said.**

Express Scripts Holding Co. Chief Medical Officer Steve Miller told the *Pink Sheet* he did expect the FOURIER results to create more demand from physicians, at least for the labeled population. "Doctors will be a bit more enthusiastic, the question is will patients want to take an injectable drug," he said.

As to whether the level in benefit in FOURIER met expectations, Miller acknowledged that "there are probably mixed feelings in the market." However, he said, "the drug showed benefit in the right direction, maybe not the benefit some were hoping for, but it was incrementally better." Miller thought that the lack of a survival advantage was largely due to study design. "The question is whether is incremental enough to justify $14,000/year," the exec said.

Repatha's current wholesale acquisition cost is $14,523, though Amgen reports the net ranges between $7,700 and $11,200 per year.

This treatment category continues to be one where both payers and drug makers are experimenting with new payment approaches. Without going into details, Miller noted that Express Scripts is "actively" working on a new program with Amgen. The pharmacy benefit manager has been working on "several ideas" with both it and Sanofi, and will continue to do so.

Amgen's Money-Back Offer To Payers

Amgen seems ready to preempt payer pushback by announcing new contracting options. "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, Amgen told the *Pink Sheet*, 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."

“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.” The company walked through how its price setting method reflects a value-oriented approach during an investor briefing from ACC. (Also see "Amgen Says Repatha Outcomes Trial Backs Up Its Pricing Math" - Pink Sheet, 19 Mar, 2017.)

Amgen's material on the outcomes-based contracts notes that contract options will be offered "to payers willing to remove access barriers."

FOURIER Findings

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. 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)

Evolocumab reduced the risk of the primary endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization by 15%, and a 20% reduction on the harder secondary endpoint of CV death, MI or stroke. However, many analysts were expecting at least a 20% reduction on the primary endpoint and a mortality benefit – which was not demonstrated in the trial.

While there was no effect overall on cardiovascular death, lead investigator Marc Sabatine, Harvard Medical School, noted there were directional trends for death due to acute MI and death due to acute stroke. 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." He similarly ascribed the lack of effect on unstable angina to the increased specificity of the assays used today,

In addition to a refund back to the payer for patients on Repatha who have a heart attack or stroke, "for what they spent on Repatha," Amgen is going to continue with other risk-sharing mechanisms that focus on LDL levels or cost predictability to the payer. Those include per-member/per-month contracts to help payers with cost predictability as volume changes over time and volume discounts.

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.)

What's The Problem?

It appears that access is not solely an issue of initial hurdles put up by payers. Other factors, such as adherence and the burden on patients' pocketbooks, also play important roles.

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 co-authors say in the March 17 publication of FOURIER results in the *New England Journal of Medicine*.

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

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 over placebo and should lower the number needed to treat to prevent an event.

The FOURIER results also confirmed Repatha's safety and the value of treating to low LDL levels, showing "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.

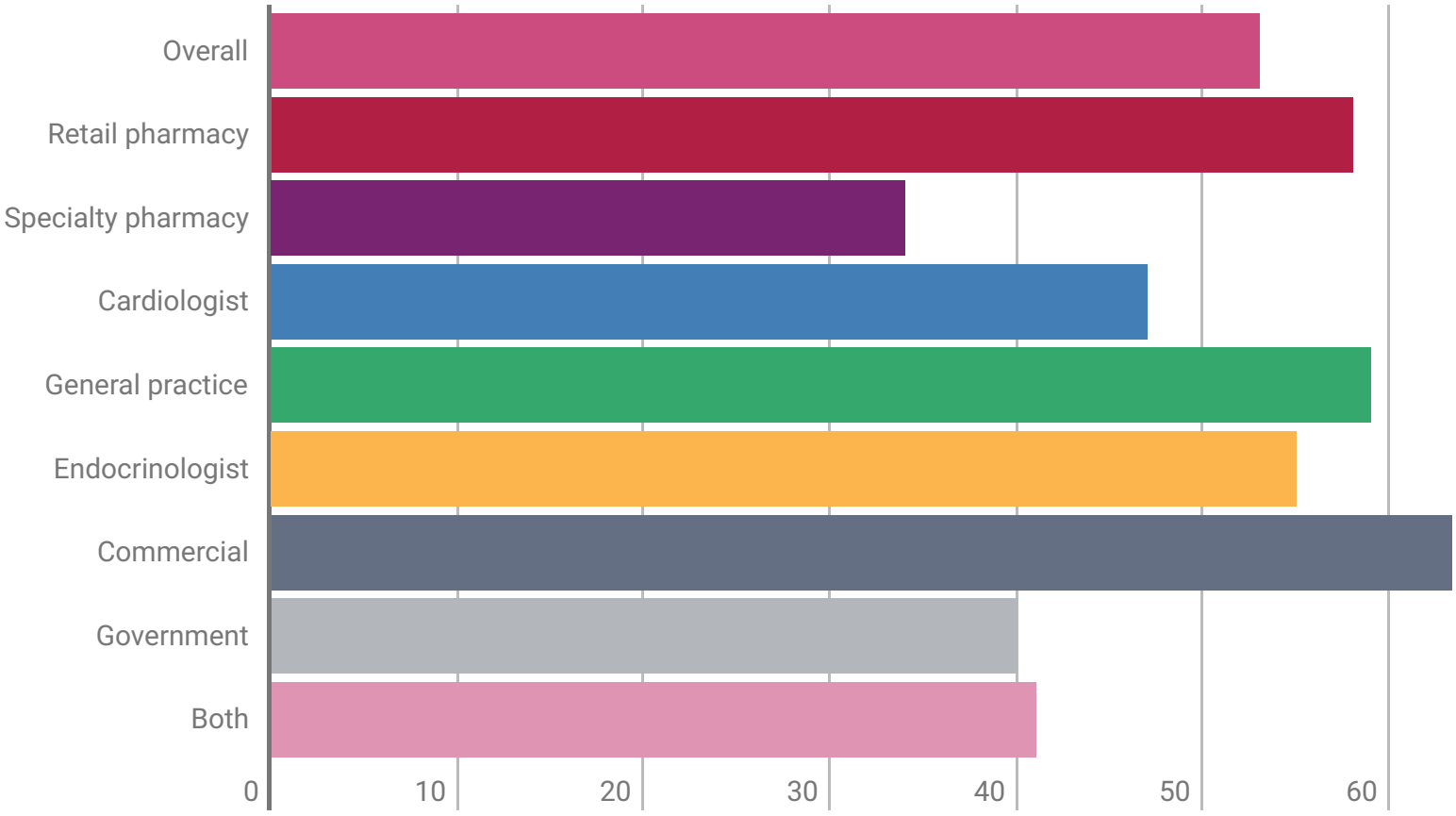
The trial showed a clean safety picture across the board, including no signal in adverse events that had been areas of concern – like neurocognition and diabetes. There were no patients with neutralizing antibodies – which proved to be a major factor for **Pfizer Inc**.'s terminated PCSK9 inhibitor bococizumab.

Both the sponsors and external sources have documented the difficulty in gaining coverage for PCSK9 inhibitors, which kept sales to $141m for Repatha in 2016. The Institute for Patient Access recently issued state-by-state health plan report cards showing rejection rates of about 50%.

Real Endpoints' Longman noted that many of the prior authorizations require patient adherence to both the PCSK9 inhibitor and the statin taken concurrently. At ACC, one poster estimated PCSK9 adherence at 59% and statin adherence can be even lower. "The PCSK9 problem is not simply a problem of PCSK9 coverage or adherence, it's a problem of statin adherence and therefore PCSK9 coverage," he said.

The Symphony Health Solutions data analysis presented March 19 by Duke's Navar showed that prescription volume has been increasing, but there has not been any improvement in payer approvals over time. The data captured 90% of retail pharmacies, 60% of mail-order and 70% of specialty pharmacies, on new prescriptions of Repatha and Praluent from Aug. 1, 2015-July 31, 2016.

PCSK9 Rx Rejection Rates



Source: A.M. Navar presentation at American College of Cardiology

Abandonment of prescriptions even after filled is high, at 34.7% of dispensed prescriptions (20.2% for commercial payers, 41.5% for Medicare). That rate was lower when a coupon program was used, Navar said, suggesting the copay is the major issue: abandoned prescriptions fell from 39.0% to 15.3% when a coupon

was used.

Rejection rates are highly variable by PBM/payer, Navar reported, ranging from 33% to 75% for the top 10 PBMs by volume.

Navar acknowledged a limitation of the analysis was that it did not look at clinical factors, and that many of the rejections are "probably appropriately rejected." But, she added, "without change [in the rejection rates] over time, I do not think this is due to clinical factors alone."

"There's a disconnect between what providers are trying to do and what happens," Navar said.

The researcher does expect trends will change now that outcomes data is available, certainly that demand for PCSK9 inhibitors will increase. "I suspect the prior authorization process currently is a very blunt instrument. Given the increased demand [from the FOURIER results] we need to look back at the prior authorization process and the burden on patients and the burden on providers," she said.

What Could Change?

Amgen reports that payers are already changing utilization management criteria and that it has "numerous" risk-sharing contracts for Repatha in place.

But changes need to occur both with specific coverage requirements and with payers' overall perceptions of the PCSK9 inhibitors' value. Additional analysis of FOURIER will be necessary and payers and providers will look to changes in treatment guidelines.

In an interview at ACC, Cleveland Clinic cardiologist Steve Nissen said he expects the next iteration of treatment guidelines to endorse PCSK9 inhibitor use in high-risk patients and suggest it be considered in patients at moderate risk. Some expect the guidelines to change in the next year, though others expect the committee will wait for the publication of Sanofi's ODYSSEY OUTCOMES trial for Praluent in a peer-reviewed journal.

Greater changes in prescribing could come once subgroup analysis is done of FOURIER to clarify the risk reduction in the "ultra high risk patients" with comorbidities like diabetes or recent events. "These patients might get faster coverage, easier coverage, and the regular high risk patients might still be covered with these somewhat challenging restrictions," Longman predicted.

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* 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 longterm 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."

"A number needed to treat calculation is not a formal health economic assessment that can represent the value of a health care intervention in a holistic way," Amgen's Ofman stressed during the investor briefing. "It's almost never used," he added, by health authorities around the world. "It counts events only, not the impact of those events."

[Editor's note: For more information, see Datamonitor Healthcare's in-depth report on PCSK9 inhibitor pricing and reimbursement.]