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# RISKY BUSINESS

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**Amgen Inc.**'s proposal to increase access to cholesterol drug **Repatha** evolocumab will hinge on increasing medication adherence rates. In addition to continuing its existing adherence programs that use electronic alerts, the biotech hopes to take a page out of the playbooks of PBMs that have developed programs for HCV.

Data presented at the **American College of Cardiology** provided grist for Amgen to persuade payers to increase access to Repatha, and also put a fine point on the challenges it will face in doing so.

The company presented detailed results from the Phase III FOURIER cardiovascular outcomes trial, which showed a statistically significant 15% reduction in the relative risk of major adverse cardiovascular events, including hospitalization for unstable angina, coronary revascularization, heart attack, stroke or cardiovascular death ($p<0.001$).

Repatha also showed a 20% relative risk reduction on a secondary composite endpoint that consisted only of heart attack, stroke and cardiovascular death ($p<0.001$).

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*Joshua Ofman, Amgen*

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Based on the data, the company has proposed to trade refunds for patients who have heart attacks or strokes for broader reimbursement of Repatha.

A different ACC presentation showed the size of the challenge.

Amgen's retrospective analysis showed prescriptions were initially rejected for 79.2% of 45,029 patients prescribed a **PCSK9** inhibitor between August 2015 and July 2016. Only 47.2% of prescriptions were subsequently approved, and only 30.9% of initial prescriptions were dispensed.

A second analysis of 44,234 prescriptions showed 83% of claims were initially rejected. This analysis looked for but did not find any major clinical characteristics linked to the rejections, suggesting inconsistency in the ways prior authorization criteria were applied.

Also in the challenge category was a presentation from Amgen and **Quintiles IMS Holdings Inc.** that showed poor adherence. The biotech's money-back offer would be limited to patients who remain on both Repatha and concomitant cholesterol lowering drugs as prescribed.

The analysis of QuintilesIMS's longitudinal prescription claims database showed that among 4,853 patients who initiated treatment with a PCSK9 inhibitor between August 2015 and January 2016, adherence was just 57%.

"We can only take a risk on the outcomes if the patients are adherent to therapy, so we'll be measuring adherence and making sure patients are maintained," said Joshua Ofman, SVP of global value, access and policy at Amgen.

## FAMILIAR TERRITORY

Repatha was launched at a WAC of $14,100 and was approved with a broad label including familial hypercholesterolemia (FH) and patients with clinical atherosclerotic cardiovascular disease who are on maximally tolerated statins.

Sales have gotten off to a slower start than the market had hoped, despite risk-sharing based on LDL reductions and utilization caps Amgen has agreed to, along with discounts and rebates that the company said have brought net prices into the range of $7,700-$10,400 per year (see "Prolia Parallels").

Most payers restricted access to patients with documented FH or a history of myocardial infarction, stroke, angina, coronary or other atrial revascularization or peripheral artery disease (PAD).

Patients without FH must also have evidence of inadequate LDL control after treatment with high-intensity

statins for more than 90 days and, in some cases, with ezetimibe.

Amgen said the data on prescription denials presented at ACC suggested that the prior authorization process has not been driven by clinical criteria.

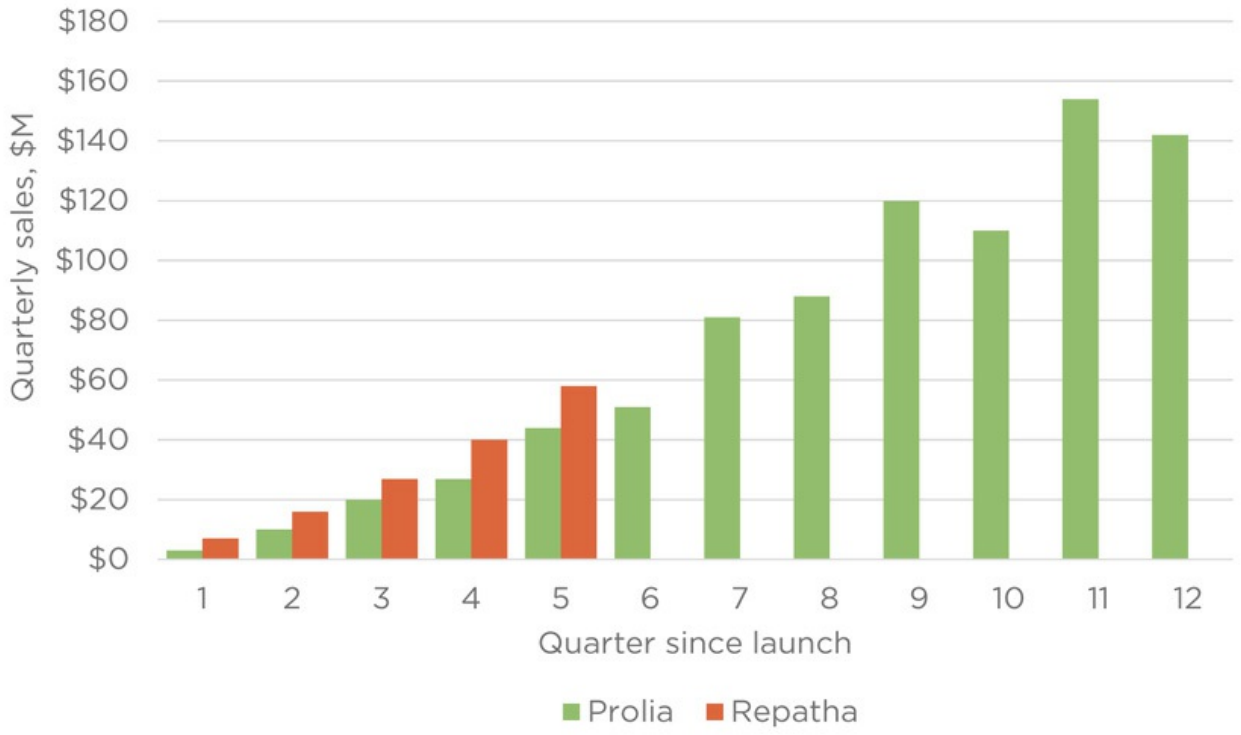
The analysis found no major differences in baseline statin use, statin intensity, ezetimibe use or history of co-medication use, including antiplatelet therapy, a clinical characteristic Amgen said is "highly suggestive of atherosclerotic cardiovascular disease."

## FIGURE: PROLIA PARALLELS

The early revenue trajectory for Repatha evolocumab from Amgen Inc. (NASDAQ:AMGN) is similar to that of osteoporosis drug Prolia denosumab, another primary care mAb from the big biotech that got off to a slower-than-expected start. Both products launched into similar conditions: large markets with generic or soon-to-be generic oral alternatives where the mAb's price was a big step up. The market had blockbuster expectations for both within the first two to three years of launch.

The price differential for Prolia, which launched with an annual wholesale acquisition cost (WAC) of $1,650, was not as big as that for Repatha, at $14,100. To stimulate Prolia sales, Amgen got the physician-administered drug reimbursed under the Part D pharmacy benefit to avoid the buy-and-bill model used for Part B drugs. For Repatha, Amgen is already offering rebates of up to 47% and has contracted for utilization caps with some commercial payers. With fresh data in hand showing a 15% reduction in the risk of adverse cardiovascular events, the biotech is now proposing to refund the cost of the drug for any patient who is adherent but experiences an MI or stroke.

Below, the first five quarters (4Q15-4Q16) of Repatha sales are plotted with the first 12 quarters of Prolia sales (2Q10-1Q13). By 2014, annual sales of Prolia eclipsed $1 billion, and in 2016 they reached $1.6 billion. *Source: Amgen SEC filings*




### ARMED WITH OUTCOMES

Amgen believes the FOURIER data justify broadening access via risk-sharing agreements based on CV outcomes.

"I think it creates a real sense of urgency to address the access problem that exists via these types of arrangements," said Ofman.

Prime Therapeutics LLC told BioCentury it is working on a new arrangement with Amgen based on CV benefits seen in FOURIER that it plans to finalize this year.

The biotech is also working with payers to simplify and streamline prior authorization criteria.

"We're only offering contracts for payers who want to improve access. The expectation is that payers will recognize the significance of the data and will take steps to simplify the process, simplify the criteria and work with us to improve the health of the population," Ofman said.

"Several payers have recognized the failure of the system that they put in place and so now we're working with

them to simplify that process," he said, but did not provide details on how the criteria were being adjusted.

Amgen's work will be complemented by campaigns patient groups are leading. On March 15, the FH Foundation and Express Scripts Holding Co. said they had collaborated to expand the PBM's coverage of PCSK9 inhibitors to treat FH.

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Prior authorization criteria from Express Scripts and other payers and PBMs required a genetic test to confirm diagnosis of FH. According to the foundation's data on 4,000 FH patients in the U.S., FH is currently diagnosed based on clinical characteristics and family history, with less than 10% of diagnoses based on genetic tests.

The foundation said that in many cases, the genetic tests, which would fall under medical benefits rather than drug benefits, are not reimbursed.

"We were able to show them how patients are being diagnosed today and work with them to help them understand what FH looks like and better capture that," said Cat Davis Ahmed, director of outreach at the foundation.

Express Scripts will now accept a clinical diagnosis and evidence of family history as an alternative to genetic testing.

"We hope that with conversations like those we had with Express Scripts and we're having with other payers, it can encourage them to be reasonable and focus on the highest-need patients," said FH Foundation founder and CEO Katherine Wilemon.

## ADHERENCE IS ALL

For Amgen, managing risk under new outcomes-based deals will require programs to keep patients adherent on Repatha and a statin. The task isn't easy, as adherence to cholesterol-lowering drugs is very poor.

Data from studies by Duke University showed only 44% of patients with documented coronary artery disease used their statins consistently over seven years.

A study published in the *Journal of the American Medical Association* in 2002 found that among adults over age 65, adherence to statins for primary prevention after two years drops to 25.4%. It is higher - 40.1% - among patients like those in FOURIER who have previously experienced a CV event.

Amgen already uses its Repatha Ready program to send electronic alerts and emails to patients to remind them to take Repatha and when to refill their prescription.

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The program includes nurses who are available via phone to provide injection training for new patients or to provide other ongoing personalized support services, including follow-up after the patient fills the first prescription and until the patient feels comfortable with the injection.

Amgen's existing risk-sharing deal with Prime is based on adherence. Amgen pays a rebate to the PBM when patient compliance on Repatha falls below an undisclosed threshold. The PBM said the arrangement does not include adherence on the statin as well.

Prime said adherence under the program has been "high," but declined to disclose details beyond saying that traditionally adherence is better on injectable specialty medicines.

Ofman said Amgen plans to work with additional PBMs that have instituted adherence programs in other areas. For instance, he highlighted Express Script's program in HCV. The PBM used its specialty pharmacy Accredo Health to achieve adherence rates of more than 95%.

Accredo provides an app that allows patients to create an individualized treatment routine and set reminders for the timing and amount of their next dose. Patients can also track their adherence and receive reminders on why its important to take their drugs on time.

Joshua Benner, president and CEO at RxAnte Inc., encouraged Amgen to also work with physicians.

"Adherence really starts in the office where the patient hears about the therapy along with the consequences of not taking it," Benner said. RxAnte works with payers to identify patients at high risk of being non-adherent.

## FIRM PRICE

Before the detailed FOURIER data were released, payers, PBMs and reimbursement consultants told BioCentury that to improve access, Repatha would have to reduce the risk of MACE by at least 20%, Amgen would have to agree to risk-sharing based on outcomes like MI - and the biotech would have to make additional net price concessions.

Amgen doesn't plan to make net price reductions on top of any new risk-sharing contracts.

"We think for the most part that the net price that people are paying today represents a good economic value, but we're also putting more innovative contracts in place where we take the risk. So if Repatha does not perform, the net price could go down more," Ofman said.

Roger Longman, CEO of reimbursement consultancy Real Endpoints LLC, is skeptical. "If payers still consider this net price to be high, it will not offset the cost for the volume of people who need to be treated," he told BioCentury.

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Based on an absolute risk reduction of 1.5% for the MACE endpoint in FOURIER, Amgen would need to treat about 67 patients to prevent a cardiovascular death, MI or stroke. That would translate into a $513,333-$693,333 cost per event avoided based on a net price of $7,700-$10,400.

Amgen conducted its own analysis based on a composite endpoint of coronary heart death, MI, stroke and coronary revascularization over five years to arrive at an absolute risk reduction of 5.9% and a number needed to treat (NNT) of 17, which would translate into a $130,900-$176,800 annual cost per event avoided.

According to a 2014 study in *JAMA*, the mean in-patient costs to treat an MI were $129,000-$245,000, while a 2014 publication in the *Journal of Stroke and Cerebrovascular Diseases* found that in-patient costs for stroke were $18,963-$32,035.

Amgen told BioCentury that an NNT analysis is not appropriate to determine a drug's value.

"This only counts events and does not take into account the impact of the events or the value of preventing events," Ofman said. For example, if the drug prevents a fatal event, it could prolong lifespan on average by 15-16 years.

Additionally, he noted that the NNT in the real world is half that in trials, because event rates are often higher in the real world. That would put Repatha's NNT closer to 33, and the annual cost to prevent an event as low as $256,667 based on a net price of $7,700.

Amgen said cost per QALY is a more appropriate measure than NNT.

Michael Sherman, CMO at **Harvard Pilgrim Health Care Inc.**, declined to say whether Repatha's net price should drop further. He said the new risk-sharing proposal from Amgen is "of interest" but added, "I don't think that alone will be sufficient to get payers to loosen criteria."

## COMPANIES AND INSTITUTIONS MENTIONED

American College of Cardiology (ACC), Washington, D.C.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Duke University, Durham, N.C.
Express Scripts Holding Co. (NASDAQ:ESRX), St. Louis, Mo.
FH Foundation, Pasadena, Calif.
Harvard Pilgrim Health Care Inc., Boston, Mass.
Prime Therapeutics LLC, Eagan, Minn.
Quintiles IMS Holdings Inc. (NYSE:Q), Durham, N.C.
Real Endpoints LLC, Westport, Conn.
RxAnte Inc., Portland, Maine

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