Pink Sheet
Pharma intelligence | informa

TAGS: Clinical Trials | Strategy | Business Strategies

PCSK9 Sponsors, Payers In The Ring At ACC

11 Apr 2016 | **NEWS**

by Emily Hayes

@emilykatehayes | emily.hayes@informa.com

Executive Summary

Cardiologists bemoaned high cost of new drugs and high hurdles for reimbursement at the American College of Cardiology annual meeting; will outcomes data save the day?

Sponsors of the PCSK9 inhibitors have been having a hard time fighting their way into the cholesterol market in their first year of launch. Cardiologists are wary of high prices for new drugs and payers have reportedly created an obstacle course for the doctors who are on board.

The build-up of investor excitement over anti-PCSK9 monoclonal antibodies in the post-*Lipitor* era was fast and heavy, despite some awareness early on in their development of the risks of launching injectables in a market dominated by oral generics, especially without outcomes data (Also see "Will New Injectables Sell In An Oral, Mainly Generic Cholesterol World?" - Pink Sheet, 9 Apr, 2012.).

With high LDL-lowering potency, good tolerability and a genetically based mechanism of action that is similar to statins, the PCSK9 class looked like a game-changer in cholesterol reduction, despite all of the available generics (Also see "PCSK9 Mechanism Lends Confidence Ahead Of Outcomes Data" - Pink Sheet, 23 Mar, 2015.).

But performance of **Amgen Inc.**'s *Repatha* (evolocumab), approved in August 2015, and **Sanofi/Regeneron Pharmaceuticals Inc.**'s competing *Praluent* (alirocumab), cleared that July, has been disappointing. Amgen hasn't broken out sales, usually a sign they are minimal, and Praluent's worldwide annual sales amounted to only $11m (Also see "Regeneron's Eylea Soars, But Praluent Is Slow Out Of The Gate" - Pink Sheet, 9 Feb, 2016.).

The PCSK9 inhibitors are part of a crop of new cardiology drugs, including **Novartis AG**' *Entresto* (sacubitril/valsartan), that are facing a lot of scrutiny on outcomes and pricing as they seek to carve out a position in the cardiology market (*see related story,* (Also see "Novartis Accentuates The Positives Of Heart Failure Drug *Entresto* At ACC" - Pink Sheet, 11 Apr, 2016.)).

A familiar refrain at the American College of Cardiology meeting, held April 1-4 in Chicago, was that the prices of new cardiology drugs are too high and that there is a very simple solution: if the drug companies lower the cost, more patients could get them. An April 2 symposium titled "PCSK9 Inhibitors and Entresto – Who should get these expensive new drugs and what are the economic implications?" tackled this topic head on.

The list price for PCSK9 inhibitors is about $14,000 a year, though competition and exclusive contracts with some insurers likely means substantial rebates in the real world (Also see "Praluent Is Only Preferred PCSK9 In UnitedHealth Plans" - Pink Sheet, 11 Dec, 2015.).

During a "Deep Dive" session at the ACC meeting on April 3 that included a presentation on Amgen's GAUSS-3 results for Repatha in statin-intolerant patients, someone commented half-jokingly that one item was missing from the list of PCSK9 inhibitor adverse events – "induced poverty."

A technology assessment of the PCSK9 inhibitors last fall by the Institute for Clinical and Economic Review (ICER) suggests that price discounts of about 50% or more would be needed for the PCSK9 inhibitors to be considered cost effective, a report that was, not surprisingly, hailed by insurance companies (Also see "PCSK9 Revised Analysis Indicates Less Price Discounting May Be Needed" - Pink Sheet, 9 Oct, 2015.) . In the final report issued in November, ICER said that the list price offered low long-term value for patients and cited a value-based price benchmark ranging from $5,404-$7,735 per year linked to long-term value, and as low as $2,177 when the short-term budget was impacted. Uncertainty over LDL as a surrogate for outcomes was a very strong factor behind the report.

During the April 2 pharmacoeconomics symposium, Mark Hlatky, a professor of health research and policy at Stanford University, cited the ICER research to suggest that PCSK9 inhibitors' pricing will have to come down dramatically for the drugs to be cost effective and to improve access.

Furthermore, he suggested that drug pricing is being based on whatever the market will bear and that companies could still get a fair return with lower prices at higher volume.

In a highly critical editorial on April 3 in the Journal of the American Medical Association accompanying the GAUSS-3 report, San Francisco General Hospital's David Waters also cited the ICER draft report to support his position.

GAUSS-3 applied a rigorous, two -part statin "rechallenge" trial design to identify patients who were truly

statin intolerant (Also see "Amgen's Statin Intolerance Study May Not Cure What Ails PCSK9 Inhibitors" - Pink Sheet, 3 Apr, 2016.).

In prior studies, investigators had taken patients at their word about statin intolerance and this was not sufficient to gain regulatory approval specifically for this group, though sponsors believe they are included in labeling indirectly.

In the 43% who were actually intolerant in GAUSS-3, Repatha offered LDL-lowering of 52.8% vs. 16.7% for the comparator, **Merck & Co. Inc.**'s cholesterol absorption inhibitor *Zetia* (ezetemibe). Both drugs were well-tolerated.

"This study does show there is a population that gets reproducible, intolerable muscle side effects due to statins," Amgen VP-Global Development Scott Wasserman said in an interview at the meeting.

However, using a draft of the ICER report, Waters argued that "using a 'willingness-to-pay' threshold of $50,000 per quality-adjusted life-year gained, a PCSK9 inhibitor would need to cost $2,600 per year to be worthwhile for a statin-intolerant patient with cardiovascular disease and an LDL-level of 70 mg/dL or greater."

Among other reasons not to use PCSK9 inhibitors, Waters also cited the lack of outcomes data.

Lowering LDL cholesterol as a surrogate for morbidity and mortality was once taken for granted, but is now up for debate. While Zetia did succeed in the IMPROVE-IT outcomes study, the data were not strong enough to warrant a label change (Also see "PCSK9 Inhibitors May Feel Effects Of FDA Judgment On IMPROVE-IT" - Pink Sheet, 25 Jan, 2016.). The failure of **Eli Lilly & Co.**'s CETP inhibitor evacetrapib to improve outcomes in the ACCELERATE study, which was also presented at this year's ACC meeting, despite 37% LDL lowering, highlights the limitations (Also see "Who Suffers From Lilly's Evacetrapib Failure?" - Pink Sheet, 12 Oct, 2015.).

Asked to comment on the editorial during an ACC press briefing, GAUSS-3 lead investigator Steven Nissen said that he appreciates alternative perspectives, but that he does not agree with the article and that the "so-called pharmacoeconomic analysis provided is highly flawed." A patient with multiple risk factors for coronary disease is an "accident waiting to happen," Nissen said. "To say that it's not cost-effective in carefully selected patients doesn't make any sense to me."

Nissen's conclusion is that the results support treatment of patients at high risk for events who refuse to take a statin, even ahead of outcomes data, which were well under way at the time of approval. Nissen also stressed PCSK9 inhibitors are appropriate after physicians have done everything they can to get a patient on a statin.

Amgen's Wasserman said that "there are some fundamental concerns with the methodology ICER proposed to come up with value-based pricing."

"I would say when we look at it there are clearly patients for which this is cost-effective. We would like to have that discussion in a public forum where people can scrutinize the data and have a strong discourse on this," the exec said.

Four Of Five Scripts Denied

As a subjective condition, statin intolerance has always been controversial, and payers have struggled with coverage (Also see "PCSK9 Coverage: Payers Wrestling With Proving Statin Intolerance" - Pink Sheet, 2 Nov, 2015.). However, Wasserman noted that access to treatment generally – including specifically labeled indications

where all utilization management criteria have been satisfied – has been a big problem and said that he is "not necessarily confident data will cure this."

Amgen estimates that four out of five prescriptions are denied on the first submission, and 75% are ultimately denied. Even patients with the genetic disorder familial hypercholesterolemia, who are prone to very high LDL-C, are having trouble getting coverage, Amgen reports.

According to the Calif.-based FH Foundation, FH patients face challenges getting coverage for medications across the spectrum, including PCSK9 inhibitors, lipoprotein apheresis and – for homozygous FH patients –*Kynamro* (mipomersen) and *Juxtapid* (lomitapide).

Beyond GAUSS-3, Amgen has two other data releases this year: one is an intravascular ultrasound study and the other is the eagerly awaited FOURIER outcomes trial.

The FOURIER study "will address one of the concerns that's out there – the unknown effect on cardiovascular outcomes – but it is clearly not going to be the be all and end all. There's a lot of work that still needs to be done in the area of making sure the right patients get access to these medicines," Wasserman said.

Sanofi/Regeneron expects the first futility analysis in its ODYSSEY Outcomes study of Praluent, based on 50% of the expected events from the trial, later this year, and a second interim analysis, pegged to 75% of expected events, could come by year's end.

Clinicians Take Up The Fight

Seth Baum, a private practice preventive cardiologist and clinical lipidologist in Boca Raton, Fla., and the incoming president of the American Society for Preventive Cardiology, said that denials are the norm even for prescriptions for patients who fit the approved indications.

Baum said that getting reimbursement for new drugs, including the PCSK9 inhibitors and new heart failure drugs, has become increasingly challenging over the last year.

"In the old days, we used to write drugs off label. Now, when we write on label, we can't get them approved," Baum said in an interview at the meeting.

Insurance companies are also regularly changing the rules for reimbursement of PCSK9 inhibitors, keeping doctors guessing, Baum said.

"They are flexing their muscles – and flexing them really strongly," he said.

Getting a drug approved often requires a peer-to-peer chat, which sometimes turns into a heated argument. It's like we are always in a battle, but most doctors are too busy to fight insurance companies, Baum said.

Speaking for the ACC in an interview after the meeting, Andrew Freeman said that it's understandable that going from a drug that costs $100 a year to $10,000-$15,000 is a challenge.

"Whenever you get a biologic involved, the cost goes up exponentially," so it is not surprising there is enormous pushback because they are very expensive, said Freeman, who serves on the ACC's best practice quality improvement committee and is director of clinical cardiology for the National Jewish Health in Denver, Colo.

Freeman also noted that cholesterol is a surrogate we still don't fully understand.

The clinician said that the vast majority of scripts for PCSK9 inhibitors are denied up front, but that most of his requests are ultimately approved, with paperwork, due diligence and sometimes peer-to-peer chats. You have to go through the steps outlined in guidelines, and jump through the hoops before you "unleash the big guns."

"The bottom line is that it can be done, but it requires very careful documentation and it requires persistence," he said.

The last set of cholesterol guidelines from the American Heart Association and the American College of Cardiology, released in 2013, heavily stress statins over non-statin therapies and move away from treating to target in favor of treating based on risk (Also see "Cholesterol Guidelines Look High And Low: Statin Market Extended At Both Ends" - Pink Sheet, 13 Nov, 2013.) .

However, Northwestern University's Donald Lloyd-Jones and colleagues have published a new algorithm that incorporates PCSK9 inhibitors. The 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk, which was published online in the Journal of the ACC on April 1, is based on a less rigorous review of evidence compared to the guidelines and is meant to be more practical and timely.

According to the new algorithm, alirocumab and evolocumab may be considered in patients with ASCVD without comorbidities on maximally tolerated statin-ezetimibe or non-statin combination therapy in the setting of documented statin intolerance, if they achieve a less-than-anticipated response with <50% reduction in LDL-C, or have LDL-C ⩾100 mg/dL. In these patients, the PCSK9 inhibitors may be considered in addition to or in place of ezetimibe as a second step to achieve further LDL-C reduction.

It may take several months for the algorithm to become familiar and used in practice, Freeman said.

A Payer's Point Of View

The UPMC Health Plan acknowledges that it has been "aggressive" with policy on PCSK9 reimbursement, as have other payers like **Express Scripts Holding Co.**, **Aetna Inc.** and **United Health Group Co.** (Also see "Praluent Is Only Preferred PCSK9 In UnitedHealth Plans" - Pink Sheet, 11 Dec, 2015.).

There aren't any outcomes data or long-term safety data for these drugs, in contrast with volumes of outcomes data on statins, said Chronis Manolis, chief pharmacy officer at UPMC, which offers commercial and government plans.

"So until we know any more, we really believe in following an evidence-based protocol [that] we've vetted with our lipidologists, our cardiologists and everybody's on board that there is a place for PCSK9s," he said in an interview.

Access is allowed for patients who have gone through evidence-based algorithms.

"We don't have outcomes data and we don't have long-term safety data. Until we do, I think what we're trying to do is reserve it for the patients that absolutely have to have it," Manolis said.

Plans are appropriately concerned with new therapies, said Roger Longman, CEO of the reimbursement intelligence company Real Endpoints. And the more a drug gets into a broad population, the more there is a need for proof that it is safe.

“I think people are erring on the side of conservatism, particularly given the cost of these drugs,” but cost is one factor and safety is another, he said.

Whether outcomes data will be enough to bring payers and more physicians on board remains to be seen. Entresto is supported by robust outcomes data and had sluggish sales in 2015.

The impact depends partly on the magnitude of benefit. A 10% reduction in risk for cardiovascular events, for example, is likely to be too small. When it comes to assessing cost-effectiveness of a particular therapy, Longman also notes that beneficiaries regularly switch providers and plans may not benefit from prevention of events that occur down the line.

Payers have a big voice and drug companies haven’t figured out how to get their message out, he added.

Real Endpoints had projected in mid-2015 that there would be difficulties with the launches and was not surprised at the low sales, due to the payers’ power in the market, based on value. It might have made more sense for the sponsors to launch first at a high price in the highest-risk patients, like those with genetic disorders and extremely high cholesterol, and build the market over time in a subtle way, as outcomes data for larger populations became available, Longman said.

“You want to maybe not go so far, so fast,” Longman said.

Cathy Kelly (catherine.kelly@informa.com) contributed to this article.