

# “The Pink Sheet”

## How Much Is A Priority Review Worth? \$67.5 Million, Sanofi/Regeneron Say

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Regulatory Update / Word Count: 1875 / Article # 00140811010 / Posted: August 11 2014 12:01 AM

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### Executive Summary

Companies' decision to purchase and redeem BioMarin's priority review voucher for their PCSK9 inhibitor alirocumab sets the first public benchmark for a voucher's value and shows the potential advantages to be gained for sponsors in a race to market.

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[Sanofi/Regeneron Pharmaceuticals Inc.](#)'s \$67.5 million purchase of a rare pediatric disease priority review voucher from [BioMarin Pharmaceutical Inc.](#) sets the first public price tag on what a four-month reduction in FDA review time is worth. However, it also renews questions about whether tropical disease vouchers can command as high a price as their pediatric voucher brethren.

The longer regulatory lead time needed for voucher redemption and limitations on the number of transfers have been seen as making tropical disease vouchers less appealing to potential buyers than those awarded for approval of rare pediatric disease treatments.

Sanofi CEO Christopher Viehbacher said as much during a July 31 earnings call, held the day after the company announced it and partner Regeneron would use BioMarin's voucher to secure a priority review for their PCSK9 inhibitor *Praluent* (alirocumab). "The rare disease voucher is considered more valuable," he said.

What the BioMarin voucher's sale will mean for [Knight Therapeutics Inc.](#), which has a tropical disease voucher for sale, and future voucher recipients remains to be seen. However, the value of future vouchers may be tied, in part, to Sanofi/Regeneron's success or failure in quickly getting alirocumab to market, as other purchasers-in-waiting gauge the strategy's usefulness.

Potential legislative changes also could boost the value of vouchers under the tropical disease program, bringing them on par with those for rare pediatric diseases.

### Four Vouchers, One Redemption

The voucher programs were legislative creations intended to incentivize drug development for tropical and rare pediatric diseases.

Companies that receive a voucher upon product approval may redeem it themselves, or sell or transfer it to another sponsor, for a priority review of an application that otherwise would qualify only for a standard review. Under the PDUFA V review program for new molecular entities and novel biologics submitted on or after Oct. 1, 2012, that means reducing total review time from 12 months to 8 months.

In establishing the pediatric program in the FDA Safety and Innovation Act of 2012, lawmakers sought to avoid some of the shortcomings and limitations identified with the tropical disease program, which was created five years earlier through the FDA Amendments Act.

Notably, a sponsor wishing to redeem a tropical disease voucher must inform FDA one year in advance, whereas only 90 days' notice is required for pediatric vouchers. FDASIA also expressly allows an unlimited number of pediatric voucher transfers, whereas FDA has interpreted FDAAA as allowing only a single transfer of a tropical disease voucher.

To date, three vouchers have been awarded under the tropical disease program and one under the pediatric program (*see chart*).

| Priority Review Voucher Awards |  |   |   |
|--------------------------------|--|---|---|
| Company                        | Product/Date of Approval                             | Disease   | Voucher Status  |
| Tropical Disease               |  |   |   |
| Novartis                       | <i>Coartem</i> (artemether/lumefantrine)<br>4/7/2009 | Malaria   | Redeemed for priority review of gouty arthritis indication for <i>Ilaris</i> (canakinumab), which resulted in an FDA "complete response" letter announced 8/29/2011 |
| Janssen R&D                    | <i>Sirturo</i> (bedaquiline)<br>12/28/2012           | Multi-drug resistant tuberculosis                                 | Company has declined to publicly disclose plans for the voucher   |
| Knight Therapeutics            | <i>Impavido</i> (miltefosine)<br>3/19/2014           | Leishmaniasis   | Company has disclosed its intent to sell the voucher  |
| Rare Pediatric Disease         |  |   |   |
| BioMarin                       | <i>Vimizim</i> (elosulfase alfa)<br>2/14/2014        | Mucopolysaccharidosis type IVA (also known as Morquio A syndrome) | Sale to Regeneron Ireland for \$67.5 million announced 7/30/2014  |

While the vouchers may ensure a speedier FDA review, they are no guarantee for approval, a lesson that **Novartis AG** learned the hard way in redeeming the tropical disease voucher earned for the April 2009 approval of its antimalarial *Coartem* (artemether/lumefantrine).

Novartis' use of the voucher in a failed bid to expand the indication for the interleukin-1 beta inhibitor *Ilaris*(canakinumab) may have dampened companies' interest in spending millions of dollars to buy another firm's voucher ("[Novartis Takes Stock Of Ilaris For Gout Following FDA's Complete Response Letter](#)" — "[The Pink Sheet](#)" *DAILY*, Aug. 29, 2011).

BioMarin secured the first rare pediatric disease voucher in February with approval of *Vimizim* (elosulfase alfa) for Morquio A syndrome, a rare, autosomal recessive lysosomal storage disease also known as Mucopolysaccharidosis type IVA (MPS IVA).

FDA appeared to show some regulatory flexibility in how it interpreted and applied the FDASIA provisions, awarding BioMarin a voucher even though Vimizim's indication is not strictly limited to pediatric patients ("[BioMarin Tests FDASIA's Pediatric Voucher Waters With Vimizim Approval](#)" — *"The Pink Sheet," Feb. 24, 2014*). The agency ultimately concluded that the Vimizim BLA represented a rare pediatric disease product application under the statute ("[Vimizim Voucher A Result Of BioMarin's Late Request, FDA Flexibility](#)" — *"The Pink Sheet," Aug. 11, 2014*).

BioMarin's development and commercialization strategy focuses primarily on treatments for rare inherited disorders that frequently lack other therapeutic options and, therefore, would be expected to qualify for priority review on their own. Consequently, it is not surprising that the company opted to sell the voucher instead of redeeming it for one of its own products.

## Sanofi/Regeneron Drop A Bombshell

However, the July 30 after-market close announcement that Sanofi and Regeneron planned to use the voucher for alirocumab was striking for a number of reasons. It not only was the first publicly disclosed sale – complete with price tag – of a priority review voucher, but the deal was intended to benefit a product competing to be the first in a high-profile class of cholesterol treatments targeting a potentially enormous patient population ("[For Regeneron, Near-Term PCSK9 Filing, Eylea Growth Point To Rapidly Improving Prospects](#)" — *"The Pink Sheet" DAILY, Aug. 5, 2014*).

Regeneron Ireland, an indirect, wholly owned subsidiary of Regeneron, purchased the voucher for a one-time payment of \$67.5 million from BioMarin GALNS, a direct, wholly owned subsidiary. Sanofi and Regeneron will share the voucher's purchase price equally.

Earlier on July 30, Sanofi and Regeneron had announced strong efficacy results for alirocumab from nine Phase III trials. More importantly, however, they reported an interim analysis from one trial that suggested a reduced risk of major cardiovascular events – supportive evidence that could give FDA more confidence in approving alirocumab prior to completion of a long-term CV outcomes trial ("[Sanofi/Regeneron's PCSK9 Inhibitor Gets Reassuring CV Data – And A Priority Review Voucher](#)" — *"The Pink Sheet" DAILY, Jul. 30, 2014*).

Sanofi/Regeneron and [Amgen Inc.](#) are at the head of the PCSK9 inhibitor development pack. Amgen has said it is working to submit its application for evolocumab to FDA in the current quarter, while Sanofi and Regeneron are targeting a submission by year-end.

It appears that Sanofi and Regeneron did not want to take any chances of falling behind Amgen. With assurance of a shortened, eight-month review that the priority review voucher brings, the development partners appear to have caught up to or moved slightly ahead of Amgen in terms of product approval goal date and market launch, assuming that both PCSK9 inhibitors are approved on a first-cycle review.

Beyond quicker time to approval, other potential benefits from using the voucher include: earlier sales on a product predicted to reach blockbuster status within a few years of launch; first-to-market advantage in negotiations with payers and securing formulary position; and a jump on physician detailing and marketing.

"The priority review voucher program was established to provide incentives that would enhance innovation in key areas of unmet patient need," Regeneron VP-Regulatory Affairs Ned Braunstein said in a press release. "Our decision to acquire and leverage the voucher is clear evidence that this program is a valuable incentive for biopharmaceutical companies."

During an Aug. 5 earnings call, Regeneron officials declined to say whether they already have given FDA the required 90-day advance notice for redemption.

## Voucher Important In Race To Market

None of the companies involved in the voucher transaction were willing to discuss details about the sale, discussions leading up to the agreement or whether there were other bidders in the mix. Consequently, much remains publicly

unknown about how Sanofi and Regeneron went about putting a price tag on a four-month reduction in FDA review time for alirocumab.

However, Duke University economist David Ridley, lead author of a 2006 article in Health Affairs that led to the creation of the tropical disease voucher program, believes the purchasers got a good deal.

"I think Sanofi/Regeneron got a bargain," Ridley said in an email to "The Pink Sheet."

"First, the voucher will narrow the launch gap between them and the competition, leading to greater market share. Second, the voucher will allow them to earn each dollar several months earlier, and a dollar received now is worth more than a dollar received later."

In an interview, Ridley said the voucher purchase makes sense because Sanofi/Regeneron are in a race to market. "The benefits to them are very clear. They're worried about being behind." The alirocumab partners also benefitted from the cautious approach of other potential voucher purchasers.

"I knew that potential buyers were being quite cautious," Ridley said. "You don't want to be the manager that sticks her neck out, spends hundreds of millions of dollars for a voucher, when the drug might not succeed."

Ridley's 2006 Health Affairs article estimated that the value of changing the review classification from standard to priority for a compound in the top 10% of sales would be worth \$322 million on average to a manufacturer, although that figure was based on a wider discrepancy between standard and priority review approval times than is now seen, Ridley said.

That estimate, however, was based simply on moving sales forward and did not take into account benefits that may be harder to quantify, such as the advantages that come with being first to market and locking in customers, he said.

"In the eyes of pharmaceutical leaders, I think that race to market has got to matter," Ridley said.

Valuation estimates for priority review vouchers have been all over the board, reaching as high as \$500 million.

While the Vimizim voucher came in well under that estimate, the transaction publicly establishes a market value for the first time, Ridley said. He expects to see the price of future vouchers increase as long as the market does not become saturated with them.

## Implications For Knight?

Knight Therapeutics holds a tropical disease voucher gained in connection with FDA's approval in March of the leishmaniasis treatment *Impavido* (miltefosine).

The NDA originally was submitted by [Paladin Labs Inc.](#), which was acquired in November 2013 by [Endo International PLC](#). As part of that deal, Paladin spun off a new public company, Knight, which held the rights to Impavido.

Knight has made clear its intention to sell the voucher, although it has cautioned that the process may take some time ("[For Sale: Knight Therapeutics Seeks Buyers For Impavido Priority Review Voucher](#)" — "[The Pink Sheet](#)" *DAILY*, Mar. 20, 2014). The firm's valuation experts have estimated the voucher's fair market value in the range of 5 million to 15 million Canadian dollars (approximately \$4.6 million to \$13.7 million).

With a public price tag now set for a rare pediatric disease voucher, Ridley preached the need for continued patience by Knight.

“If I were in their shoes, my reaction would be: ‘We may need to be patient,’” he said. “First, wait until another firm comes along that’s in a race [to market] and keep talking to firms. I know there are multiple big pharmaceutical manufacturers that have been thinking about a purchase of a voucher. You just need to keep having those discussions and stay on the radars of these big pharmaceutical manufacturers.”

Ridley said the value of tropical disease vouchers could get a boost from potential legislative changes to the program’s notification and transfer requirements, which would bring them in line with those of the pediatric program. He has had preliminary conversations with congressional staffers on this subject and is working on some related analyses.