worsening heart failure." However, Temple and others didn't think the rationale for when and how physicians decided to treat patients for worsening heart failure was spelled out with sufficient rigor to support a Serelaxin approval. If the sponsor had gone with something more straightforward, Temple added, "it would have been a positive study." Later in the meeting, Temple said that an endpoint in reduction of hospitalization "would be a reasonable design."

"We really believed we'd tried to find a way to explain a complicated benefit," Nathwani says. Plus, FDA had reviewed the protocol or statistical plan for RELAX three times, he says, and had no comments about the fact that worsening heart failure was embedded in the primary endpoint and was also an independent exploratory endpoint. As a result, "We were surprised by the reaction that we received," he says.

Nonetheless, the advisors were encouraging. "I think the drug may do better than the investigators thought it would," summarized committee member James DeLemos of the University of Texas Southwestern Medical Center in Dallas. "They went out to find a drug that only improved symptoms. [It] didn't really do that but it affects harder outcomes in a more meaningful way and they weren't really designed to test that adequately with rigorous endpoints and sufficient numbers. It's possible that the drug may do more than was intended in the original trial with regard to measurable outcome."

"There's real potential for this drug to improve worsening of heart failure, potentially shorten hospital stay, [and] potentially improve both renal and troponin biomarkers," added Philip Sager of Stanford University in Palo Alto, California. "But I don't think any of them go beyond hypothesis generating."

Serelaxin's rationale in heart failure stems from the role the hormone plays in pregnancy. It is produced in the ovaries and placenta and goes up during pregnancy to help the cervix and uterus expand. (Relaxin is also found in men at low levels, with higher concentrations in the prostate.) Within minutes of administration, Serelaxin causes vasodilation by phosphorylation of nitric oxide (NO) synthase and production of NO. (NO is released from endothelial cells and acts on adjacent smooth muscle cells to cause rapid relaxation.) Also, within hours, it induces a sustained NO-mediated vasodilation through increased endothelial endothelin type B receptors.

Cardiac output goes up by about 20% in pregnant women, systemic vascular resistance drops markedly by about 30% and renal blood flow goes up by 17%, Nathwani says, and yet they clearly don't develop heart failure in the normal course of pregnancy. "Something during pregnancy is clearly accommodating that without causing increasing strain to the myocardia and to the kidneys," he says. Relaxin, he goes on, has been the primary driver of these vascular and renal changes.

"In the first 48 hours we see a profound change in several key biomarkers which are shown—not just in our study but in others—to be prognostically important in outcomes," Nathwani says. These include changes in levels of the cardiac markers troponin and BNP (B-type natriuretic peptide) and changes in kidney function such as estimated glomerular filtration rate. "The early separation in [these] outcomes is actually a plausible reason why we are having an impact," he says.

The change in troponin is most important, he says. "We saw a change in the categorical level of 20%, which is the level used to predict myocardial infarction." A number of patients crossed that threshold in the placebo group. "Something is happening where we are stabilizing the loss of myocytes," he says. "No other vasodilator in the same groups of patients has shown a change in those biomarkers, worsening heart failure or a change in outcomes."

The relaxin saga continues. Based on the advisory committee discussion, whether or not to escalate worsening heart failure into a more significant endpoint in RELAX-2 is "certainly something we are considering deeply," says Nathwani. "It's an active and urgent discussion," he says. Novartis is also in discussions with regulators in the EU for a reexamination for conditional approval of Serelaxin by the Committee for Medicinal Products for Human Use (CHMP), which issued a negative opinion on the drug in January.

Failure to gain rapid approval for Serelaxin in acute heart failure may have disappointed Novartis. But just days after the negative advisory committee vote, Novartis cheerfully announced the early closure of a phase 3 study of another heart failure drug, the angiotensin receptor neprilysin inhibitor, LCZ696, when that drug met its primary endpoint. "We now have compelling evidence that supports LCZ696 as a new cornerstone in the management of chronic heart failure," principal study investigator Milton Packer of Southwestern Medical Center said. Novartis hopes LCZ696 and Serelaxin will offset the patent expiration of its mainstay cardiovascular drug Diovan (valsartan).

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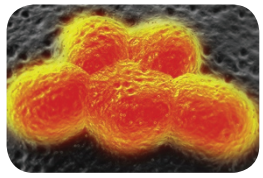
First vanguard anti-MRSA agent approved



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MRSA 'superbugs'

US Food and Drug Administration (FDA) officials green-lighted a new drug to treat skin infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). The approval is the first in a series of next-generation antibiotics coming to market after years of neglected investment in the space. Chicago-based Durata Therapeutics' antibiotic Dalvance (dalbavancin) is a glycopeptide agent, designed as an improved alternative to vancomycin. Dalvance is also the first drug with Qualified Infectious Disease Product designation—which grants an additional five year market exclusivity—to receive agency approval. Another agent for treating skin infections caused by *S. aureus* or other Gram-positive bacterial pathogens, Cubist's Sivextro (tidezolid), was expected to be approved on June 20 following an earlier unanimous recommendation by the FDA's advisory committee. Sivextro belongs to the oxazolidinones class and will be competing with linezolid (Pfizer's Zyvox), although Sivextro is considered safer and easier to administer, with once-daily instead of the twice-daily oral or intravenous dosing of Zyvox. Meanwhile, Dalvance appears to be curative when dosed twice, a week apart, but with a rather narrow spectrum of activity, mainly against *S. aureus*. Although both these candidate antibiotics were brought to FDA specifically to treat acute skin and skin structure infections, they are likely to be used more broadly, particularly to deal with antibiotic-resistant infections in other indications. Indeed, a report released late in April by the World Health Organization (WHO), "Antimicrobial resistance: global report on surveillance," provides a global perspective on this "major threat to public health," documenting resistance to antibiotics, "especially 'last-resort' antibiotics, in all regions of the world." Although the WHO report calls for measures that will lower the need for such drugs, it also urges the development of new antibiotics. Industry is taking greater heed of that message. In April, for example, Spero Therapeutics in Cambridge, Massachusetts, forged an alliance with Roche to further its development of an antimicrobial drug that targets *Pseudomonas aeruginosa*, a Gram-negative bacterial pathogen. Separately, Euprotec in Manchester, UK, in May entered into an alliance with Cantab Anti-infectives near Cambridge, UK, to develop antibiotics to treat multidrug-resistant Gram-negative bacterial infections. On April 30, the European commission approved Otsuka's Deltyba (delamanib) to treat multidrug-resistant tuberculosis.

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