

ARCA Discovery's Drug, Dx NDA for Bucindolol Could Spawn PGx Future for Other Beta Blockers

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By Chris Womack

ARCA Discovery last week announced that it would file a new drug application for its heart-failure beta-blocker bucindolol, and it will include data concerning the use of a genetic test for responders made by an undisclosed diagnostic company.

The development is noteworthy because the drug-diagnostic set could contribute to a pharmacogenomic future for treatment with beta blockers, one of the most commonly prescribed drug classes in the world.

A former Bristol-Myers Squibb compound, bucindolol could become another example of a product that has been discarded by a large drug maker only to be repositioned by a smaller firm using pharmacogenomics. In this case, ARCA found that individuals who are homozygous for the Arg-389 polymorphism in the beta-1 adrenergic receptor gene respond well to the drug. However, individuals who are heterozygous or homozygous for the Gly-389 version of this gene will not respond to this drug.

If bucindolol and its test weather the approval process, ARCA and its diagnostic partner hope to share a lucrative slice of the heart-failure market, and they may even open more beta blockers to pharmacogenomic treatment. But there is no guarantee that ARCA will be able to distinguish bucindolol from the more than 20 other beta blockers battling for market share.

"We'll hopefully file [an NDA] by the end of the year; the timeline has it going in in December," Michael Bristow, ARCA's president and CEO, told Pharmacogenomics Reporter last week.

ARCA has been working with a diagnostic company to develop a genetic test of the beta-1 adrenergic receptor to complement the drug, but the company is interested in handing it off to a partner to complete, Bristow said.

“We’re close to completing a deal with someone who’s quite capable,” he added, without elaborating. The diagnostic will have a new owner “within 30 to 60 days,” Bristow estimated.

According to Bristow, the final diagnostic will probably rely on a “TaqMan-type” real-time PCR platform. It will probably begin as a homebrew assay and be superseded by an FDA-cleared kit. There is currently no commercially available genetic test involving the beta-1 adrenergic receptor.

According to the American Heart Association, there were approximately 5 million heart failure patients in 2003. Around 550,000 of these were new cases, and about 80 or 90 percent of them are prescribed beta blockers, Bristow said.

He said ARCA hopes its drug-diagnostic product will be applicable to an estimated 600,000 patients who carry an Arg-389 allele of the beta-1 adrenergic receptor.

The competition among beta blockers for chronic heart failure is fierce. Of the 20 or so existing drugs, the two top products are GlaxoSmithKline’s Coreg and AstraZeneca’s Toprol-XL, which generated \$1.03 billion and \$1.5 billion in sales last year, respectively, according to pharma tracking firm IMS Health.

Bristow and Stephen Liggett, a researcher at the University of Maryland, Baltimore, reported the benefits patients received when prescribed bucindolol in the July 14 Proceedings of the National Academy of Sciences. The article included a retrospective analysis of 1,040 heart failure patients in the Beta-Blocker Evaluation of Survival Trial supporting a pharmacogenomic role for bucindolol. Along with a more comprehensive genetic sub-study of the BEST trial and other data, the paper forms some of the basis for ARCA’s coming NDA.

The part of the NDA supporting the beta-1 adrenergic receptor diagnostic will come from internal prospective validation conducted by ARCA’s diagnostic partner, said David Port, the company’s vice president of research and technology. ARCA is “hoping to negotiate [with the FDA for] a label with pharmacogenomic indications” that directs clinicians to the diagnostic — even if the diagnostic is only available initially through a central laboratory, he said.

One of Liggett and Bristow's hypotheses is that some of the variability in response may be due to genetic factors, and the beta-1 adrenergic receptor might be a good candidate because it is the major target of all beta blockers. They tested this hypothesis with bucindolol.

The article shows that bucindolol is effective for patients who test homozygous for the Arg-389 allele, although not extraordinarily effective, said Lanfear. Existing beta blockers are approximately as effective in general patient populations, he said.

However, he cautioned that researchers cannot draw an accurate conclusion on this matter without directly comparing the effects of bucindolol in patients known to be homozygous for the Arg-389 allele against an unselected cohort given another beta blocker. Such a study has not been conducted.

The study showed that patients homozygous for the Arg-389 polymorphism in the beta-1 adrenergic receptor gene experienced a 38-percent reduction in mortality when given bucindolol versus placebo, and a 34-percent reduction in mortality or hospitalization when given bucindolol versus placebo.

However, patients carrying just one Gly-389 version of beta-1 adrenergic receptor showed no clinical response to the drug compared to placebo.

Bucindolol's effect on mortality rate is "approximately in line with what was seen in previous beta blocker trials," said Lanfear. For example, researchers obtained similar results in the MERIT HF trial of Toprol-XL, the US Carvedilol Heart Failure Study of Coreg, and the Cardiac Insufficiency Bisoprolol Study 2 involving Merck's Zebeta, he said.

"They were all in the 30-percent risk reduction [range], except for the US Carvedilol trial, which showed a 65-percent relative risk reduction," said Lanfear. "I don't think there's an advantage to bucindolol over other beta blockers; that definitely has not been proven."

“I think the importance of the paper is that ... personalized medicine might be a better approach” in heart failure treatment, according to Douglas Mann, chief of cardiology at the Texas Heart Institute and Baylor College of Medicine.

In general, about 20 percent of patients don't respond to treatment with beta blockers while others get worse, he said. There is no genetic link proven for response to beta blockers other than bucindolol. However, “it's certainly worth testing the hypothesis that we may be able to identify [responding] patients ahead of time,” he said.

It may turn out that these patients carry the Gly-389 allele that is linked to lack of response to bucindolol, he added.

“It's going to take further study to figure out” whether the Gly allele of the beta-1 adrenergic receptor is linked to response to other beta blockers,” Liggett said. But because the gene is important to bucindolol response, “you would think that it would.”

Liggett said he and colleagues have “some studies underway” to examine the effects of beta-1 adrenergic receptor and other genes on response to other beta blockers.

“We hope [fewer] than 10” genes are involved, he said. “That would mean that within the next few years we can come up with a kind of scorecard. My question is whether pharma is going to do it ahead of time or not - I would hope pharma would want to push forward,” he added.

Coreg works in such a broad population that there's little need to look for genetic determinants of response, a GSK spokesperson said this week. The company has no plans to pursue such a diagnostic to identify responders, he added.

It may also not be in GSK's best interest to pour more research into Coreg — it loses its patent protection in 2007.

An AstraZeneca spokesperson said the company has not pursued the use of pharmacogenomic tests with its beta blocker.

When asked whether ARCA is exploring marketing the beta-1 adrenergic receptor diagnostic for other purposes, such as predicting response to other beta blockers, Bristow said, “We won’t be, but I suspect that the owner of [the diagnostic for beta-1 adrenergic receptor] — once we basically sell it — will be interested in what other settings this polymorphism might modify outcomes or therapy.”

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