Failed heart drug could be a 'genetically targeted' success

By Steve Sternberg, USA TODAY
A heart failure drug that was shelved because it failed its biggest scientific test may launch a new era of genetically targeted medicine for heart disease, researchers reported Monday.
The drug, bucindolol, did no better overall than a placebo in a 2,700-patient study that ended in 1999. But a new analysis of the trial's data suggests that the drug may cut heart failure deaths by 38% for patients with a certain genetic mutation.

"If we're successful, this will be the first genetically targeted cardiovascular drug," says the University of Colorado's Michael Bristow, a lead author of the study in today's *Proceedings of the National Academy of Sciences*.

Some experts contend that the evidence is too flimsy to support the researchers' claims. They also question the need for a targeted approach to therapy when other drugs in the same class extend survival in a broad spectrum of patients. Bucindolol won't work in everybody because the gene variant is present in half the population and is rare in blacks.

Undaunted, supporters have formed a company, Arca Discovery, to develop the drug, obtained a license to produce it and raised $15 million from venture capitalists to bring it to market. They're also working to produce a market-worthy test that will enable doctors to figure out who will benefit from treatment, Bristow says.

Bucindolol is a beta blocker, a class of drugs that protect the heart by easing its workload. Another beta blocker, carvedilol, sold as Coreg, has become a mainstay of heart failure treatment. In a study of 2,289 patients, carvedilol cut the death rate by 35% over patients taking a placebo.

The bucindolol and carvedilol studies both appeared on May 31, 2001 in *The New England Journal of Medicine*. In an accompanying editorial, Eugene Braunwald of Brigham and Women's Hospital said the gulf between the drugs isn't as vast as it might seem. Although bucindolol didn't cut the death rate overall, it did help non-blacks, he wrote.

Bristow and Stephen Liggett of the University of Maryland looked for a genetic difference that could explain why the drug helped some patients and not others. They found a single mutation in a gene for beta receptor, a biochemical switch that governs the heart's workload. Patients with the gene variant respond better to bucindolol than those who don't, the study found.

Heart failure expert Milton Packer of the University of Texas Southwestern Medical

Center says positive findings in such secondary analyses are most likely a result of chance and not the drug's effects.

The government is unlikely to "approve this drug on the basis of a retrospective analysis of a trial in which the primary outcome was that the drug didn't work," especially when other, more effective drugs are available, he said.