Strategy

Funding the white space

By Andrew Fisher
Staff Writer

Celladon Corp. found no pharma partners for its Mydicar gene therapy following data from a small Phase I/II trial in advanced heart failure patients, but the results prompted the venture arms of three of the pharmas to take a stake in the biotech based on early signs of efficacy in a population with few options.

Mydicar is a recombinant adeno-associated viral (AAV) vector carrying the gene for sarcoplasmic reticulum ATPase Ca++ transporting cardiac muscle slow twitch 2 (ATP2A2; SERCA2A). The gene is a regulator of myocardial contractility.

"At the end stages of heart failure, the muscle cells go into a survival mode," which results in a down-regulation of the SERCA2A protein, said President and CEO Krisztina Zsebo.

In attempts to improve cardiac muscle contractility, she said, "many pharmas tried to use small molecules. But they failed because the protein is down-regulated and deep inside the cell."

Current treatments for advanced heart failure include inotropic agents, which increase myocardial contractility, implantation of a left-ventricular assist device (LVAD) or a heart transplant. The drugs have modest efficacy while the other procedures are highly invasive.

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> **Krisztina Zsebo, Celladon**

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In 2011, Celladon published in *Circulation* that the nine patients receiving the highest dose of Mydicar met the primary endpoint in the open-label Phase I/II CUPID trial. The trial enrolled 39 patients with advanced, chronic New York Heart Association (NYHA) Class III-IV heart failure. This includes a large percentage of patients with congestive heart failure (CHF).

The primary endpoint was an improvement at six months in at least two of four efficacy domains, or improvement in a composite of clinical outcomes.

The symptomatic domain included measurements of NYHA class and Minnesota Living With Heart Failure Questionnaire (MLWHFQ) scores.

The functional domain measured 6-minute walking distance and change in VO2 max (a measure of exercise capacity).

The biomarker domain measured levels of N-terminal pro-brain natriuretic peptide (NT-proBNP).

The left ventricular function domain measured end-systolic volume and ejection fraction.

To meet the primary endpoint, improvement in two or more domains also had to be accompanied by: at least a positive trend in all other domains; no clinically significant worsening on any other endpoint; and, for the group level analysis, at least numerical superiority to placebo in all other domains.

The p-value for meeting the primary endpoint was set at <0.2.

According to the company, by requiring Mydicar to show improvement in two or more domains at the p<0.2 level, the likelihood the compound's effect was due to chance would actually be lower than for a single domain improvement at the more traditional p<0.05 level.

High dose Mydicar met the p<0.2 threshold in the 6-minute walking distance measure and both LV function measurements in the group level analysis.

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Canada of $3.7 billion for Enbrel, while Amgen announced sales of $3.7 billion in the U.S. and Canada.

Similar to Humira, Remicade and Enbrel are approved for at least four additional indications. Remicade is approved to treat Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis. Enbrel is approved for juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

Galapagos is hoping Abbott can expand the indications for GLPG0634 like it did with Humira.

"Abbott has explored additional indications, and we are confident they will do that again to maximize the market for the drug," van de Stolpe said.

Galapagos expects to deliver the Phase II data package to Abbott in 2014. The biotech retains co-promotion rights in Belgium, the Netherlands and Luxembourg.

COMPANIES AND INSTITUTIONS MENTIONED

Abbott Laboratories (NYSE:ABT), Abbott Park, Ill.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Galapagos N.V. (Euronext:GLPG; Pink:GLPYY), Mechelen, Belgium
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Incyte Corp. (NASDAQ:INCY), Wilmington, Del.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Cambridge, Mass.

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The low dose met the hurdle in the NYHA class and 6-minute walking distance measurements, but was associated with clinical worsening in the biomarker measurement. The middle dose met only the NYHA class measurement.

Celladon also said the compound met the clinical outcomes endpoint, which measured the composite of death, LVAD implantation or heart transplant.

An additional pre-specified analysis showed high-dose Mydicar significantly reduced the risk of multiple clinical events from baseline to 12 months by 88% compared with placebo (p=0.003). Events included worsening heart failure, myocardial infarction, LVAD implant, heart transplant and death.

The duration of cardiovascular hospitalization was 0.2 days for high-dose Mydicar vs. 2.1 days for placebo (p=0.08, not significant).

With published data in hand, Celladon went looking for a partner. The company "did a lot of due diligence with pharmas, but the trial was only in 39 patients, not enough to get over the hurdle, so a number sent us to their venture arms," said Zsebo.

The result was last month's $43 million series A-1 round, which was led by new investor Pfizer Venture Investments. Other new investors were Lundbeckfond Ventures; Novartis Venture Funds; H&Q Healthcare/Life Sciences Investors; and GBS Venture Partners. All of the company's existing investors also participated, including Enterprise Partners Venture Capital; Johnson & Johnson Development Corp.; and Venrock Associates.

Pfizer Venture's Barbara Dalton became chairman of Celladon. Lundbeckfond's Johan Kordel, Novartis Venture's Lauren Silverman, H&Q's Daniel Omstead and GBS's Josh Funder also joined the board.

Drew Senyei of Enterprise Partners remains on the board, while Venrock's Tony Evnin and Asish Xavier of J&J Development became board observers.

The round recapitalized the company, although details were not disclosed.

Zsebo said none of the pharma VC investors received an option to license Mydicar.

"When it's time to divest Celladon's assets, they will go to the highest bidder," Kordel said.

Celladon will use the money to advance Mydicar through a larger trial. The company is still formalizing the trial's design, and has not determined the size or phase of the study. Zsebo did say that based on the Phase IIa data, the company will focus on clinical outcomes as endpoints.

Celladon received exclusive rights to the AAV technology for Mydicar from Targeted Genetics Corp. in 2009. The companies had partnered in 2005 to develop AAV-based therapies for congestive heart failure *(see BioCentury, March 16, 2009)*.

Targeted Genetics changed its name to **AmpliPhi Biosciences Corp.** last year after acquiring Biocontrol Ltd. AmpliPhi is now developing Biocontrol's pipeline of bacteriophage antibiotics.

COMPANIES AND INSTITUTIONS MENTIONED

AmpliPhi Biosciences Corp. (Pink:APHB), Richmond, Va.

Celladon Corp., La Jolla, Calif.