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Renova's Gene Therapy To Reverse Heart Remodeling In CHF

Reversing the "remodeling" of the heart in congestive heart failure with an investigational gene therapy is one of the aims of the San Diego-based biotech that is planning late-stage clinical development.

Renova Therapeutics' potential gene therapy RT-100 has shown beneficial effects on the heart function of patients with congestive heart failure (CHF) in a Phase II study, Kirk Hammond, company co-founder and professor of medicine at the University of California, San Diego reported at the European Society of Cardiology annual meeting in London on Sept. 1.

RT-100 is a first-in-class, single-dose treatment that has the potential to halt and reverse the CHF-induced remodeling of the heart, rather than just slowing progression or minimizing symptoms, Renova said.

"The beneficial effects of RT-100 on heart function and ejection fraction are particularly important for CHF patients, and we will meet with regulatory authorities in the coming months to pursue late-stage clinical development and product approval," said Renova's CEO and co-founder Jack Reich in a same-day interview.

Renova conducted its current Phase II study of RT-100 as part of a public-private partnership with the US National Institutes of Health, that "if not completely unique, it's extremely rare," Reich noted. Renova has been financially supported so far by a group of high-net-worth individuals, and has not taken any venture capital money.

The individuals are able to fund further development, although the company is in discussions with potential development partners for both RT-100 and a second gene therapy product for type-2 diabetes, which is expected to enter clinical studies in 2016, Reich said.

No Safety Concerns

In a placebo-controlled study undertaken in seven medical centers in the US in patients with low ejection fraction CHF, the therapy was found to be safe and with no safety concerns in the 42 patients who received the gene therapy, Hammond said. There were no increases in heart rate, blood pressure or arrhythmias, and only a few reports of increased troponin I related to manipulation of the catheter in the coronary artery.

There were several primary endpoints in the study. With the two highest gene therapy doses, groups 4 and 5, there were statistically significant beneficial effects on ejection fraction associated with RT-100 administration that were more prominent at higher doses. A number of patients achieved normal ejection fractions, an effect not usually reported with other investigational CHF therapies, according to Reich.

There also were statistically significant improvements in another heart function measure called negative dP/dt associated with RT-100 therapy. This is a direct measure of a heart's ability to relax as part of its pumping mechanism. The time-spent-on-a-treadmill endpoint showed a marked improvement with RT-100 but this was not statistically significant, due to a large placebo effect, the company said.

The study was only conducted in 56 patients, so it was thought unlikely to show statistically significant beneficial effects on morbidity and mortality – and that proved to be the case, although the results showed promise. The gene therapy was associated with a hospitalization rate for CHF of 9.5% in the first year after therapy, compared with a 28.6% hospitalization rate in the placebo group, a 67% decrease in favor of RT-100 but not quite statistically significant. The same applied to mortality, with a 7.1% annual mortality rate due to CHF in pla-

cebo treated patients and no deaths in the first year due to CHF in the 42 patients treated with RT-100.

The RT-100 results are a rare piece of good news for the gene therapy area which recently has suffered from setbacks: Avalanche Biotechnologies Inc. reported last month that it was going back to preclinical work on its wet age-related macular degeneration product AVA-201 because of poor initial clinical results and another company, Celladon Corp. said it was halting development of gene therapy Mydicar, also because of poor clinical results (*"Celladon's Mydicar Fails In Phase IIb, But Don't Count Out Gene Therapy" — "The Pink Sheet" DAILY, April 27, 2015*).

Despite these setbacks, big pharma is showing increasing interest in gene therapy: a couple of months ago, Biogen entered into a $1bn deal with AGTC involving gene therapies for ophthalmic conditions. And GlaxoSmithKline PLC filed for approval of a gene therapy for ADA-SCID in Europe earlier this year (*"GSK Is First Big Pharma To Seek Gene Therapy Approval, Plans More" — "The Pink Sheet" DAILY, May 7, 2015*).

Reich has a long history in the gene therapy field and retired after the sale of his previous gene therapy company Collateral Therapeutics Inc. to Schering AG (now part of Bayer AG) back in 2002. "I thought I retired for good, but in 2009 I was approached to lead Renova, and after my own due diligence I was convinced RT-100 is a gene therapy product that would work."

RT-100 is based on the pioneering work of Hammond who discovered the enzyme adenylyl cyclase type 6 (AC6) was down-regulated in the heart cells of patients with CHF. AC6 appears to play an important role in heart function that is independent of its effects on cyclic-AMP. In preclinical studies, the AC6 gene has been delivered into heart cells by a modified adenovirus vector, Ad5, which is taken up by myocytes and remains in the cytoplasm without reproducing.

Also key to the potential benefits of RT-100 is that myocytes do not usually undergo cell division, and so the effects of the gene therapy are not expected to decline over time, unlike some other investigational gene therapies (*"Gene Therapy: Cures Within Reach" — START-UP, July 2015*).

Renova also has developed a proprietary delivery method for the virus vector based on cardiac catheterization that is able to deliver large amounts of the virus vector to target cells. Instead of 1%-3% of heart cells taking up virus, as seen with other delivery methods, Renova's method is associated with around 40% of target myocytes taking up the gene.