

## RT-100 (AC6 gene transfer) fact sheet

as of May 2017

### THERAPEUTIC OVERVIEW

Renova™ Therapeutics' lead product candidate, RT-100 for congestive heart failure (CHF), is a first-in-class, single-dose treatment designed to safely improve heart function.

More than a decade of intensive research shows that RT-100 has the potential to substantially benefit ailing hearts without the well-known drawbacks of many current heart failure therapies.

Our co-founder, Dr. H. Kirk Hammond, discovered that AC6 (adenylyl cyclase type 6) was down-regulated in the hearts of CHF sufferers. AC6 is a protein found in heart muscle cells that regulates heart function. Dr. Hammond and his colleagues developed a method of gene transfer designed to up-regulate AC6 content in the heart. This is the basis for RT-100.

### HOW RT-100 WORKS

RT-100 is an investigational gene therapy product that is infused during cardiac catheterization – a commonly performed outpatient procedure similar to an angiography – directly into the arteries that feed the heart. This method of gene transfer has been shown to safely and efficiently deliver AC6 directly to heart muscle cells. The gene encoding human AC6 is delivered via a modified adenovirus vector that is able to enter the cells but cannot reproduce itself (Ad5.hAC6). The AC6 is taken in by the heart and has been shown to persist in heart muscle cells. Unlike small molecule drug treatments, which work to decrease demands on the body, this gene therapy is aimed at improving overall heart function. Rather than slow progression or minimize symptoms of CHF, RT-100 has the potential to halt and reverse the CHF-induced remodeling of the heart, enabling it to pump more effectively.

### PRECLINICAL STUDIES

In extensive preclinical studies of CHF, a one-time administration of AC6 gene transfer safely improved heart function, sustained the improvement and reversed the CHF-induced remodeling of the heart, protecting it from further CHF-related damage. These results supported a Phase 2 clinical trial in heart failure patients. The National Institutes of Health's (NIH) National Heart, Lung, and Blood Institute awarded funding for the preclinical studies and subsequently the Phase 2 clinical trial.

### PHASE 2 CLINICAL TRIAL

The Phase 2 clinical trial of RT-100 – funded via a public-private partnership between the NIH's National Heart, Lung, and Blood Institute and Renova Therapeutics – assessed the safety of five doses of Ad5.hAC6 versus placebo in patients with symptomatic heart failure. Results from the study – directed by Dr. Hammond and [published in the Journal of the American Medical Association \(JAMA\) Cardiology](#) – indicate that **a one-time administration of AC6 gene transfer safely increases heart function beyond optimal heart failure therapy.**

The randomized, double-blind, placebo-controlled trial included 56 patients who were studied for up to one year at seven medical centers throughout the United States. Forty-two participants received Ad5.hAC6; 14 received a placebo.

The trial demonstrated that two endpoints showed differences between the two highest doses of AC6 (combined) versus placebo:

- AC6 gene transfer increased left ventricular peak  $-dP/dt$  ( $p=0.029$ ). This is a direct measure of the heart's ability to fill.
- AC6 gene transfer increased left ventricular ejection fraction in participants with non-ischemic heart failure ( $p=0.024$ ). Non-ischemic heart failure is a type of heart failure not associated with extensive coronary artery disease.

Symptoms of heart failure were reduced 12 weeks after therapy in the AC6-treated group but not in placebo subjects ( $p=0.0005$ ).

Although this initial study was small, the data suggest potentially promising benefits in morbidity and mortality with RT-100, which were key safety measures in the Phase 2 trial: After one year of follow-up, one death of 42 (2.4%) in the AC6-treated group and one death of 14 (7.1%) in the placebo group had occurred. The annual heart failure hospital admission rate was 9.5% in the treatment group versus 28.6% in the placebo group.

#### NEXT UP: PHASE 3 CLINICAL TRIAL - FLOURISH

Renova Therapeutics plans to conduct a randomized, placebo-controlled, double-blind multicenter Phase 3 trial of a one-time intracoronary administration of RT-100 for patients with heart failure and reduced left ventricular ejection fraction. The primary endpoint will be the reduction of the event rate of all – first and repeat – heart failure hospitalizations occurring after RT-100 intracoronary injection from baseline to 12 months (the study period). Patient safety will continue to be monitored during a follow-up period following completion of the study.

This pivotal trial – known as **FLOURISH** (Heart Failure with Reduced Left Ventricular Ejection Fraction: One-time Gene Transfer Using RT-100 – Incoronary Administration of Adenovirus 5 encoding Human AC6) – is expected to commence in the second half of 2017 across 60 medical centers in the United States.

#### ABOUT CONGESTIVE HEART FAILURE

CHF, often simply known as heart failure, is a chronic disease characterized by the inability of the heart to pump sufficient blood to meet the body's demands. It is a progressive and fatal chronic disease, and symptoms worsen over time. CHF can be caused by many conditions that damage the heart muscle, including heart attacks, infections, alcohol or drug abuse, as well as high blood pressure, valve disease, thyroid disease, kidney disease, diabetes or heart defects present at birth. People with severe CHF may need a mechanical heart pump or a heart transplant.

##### *Prevalence and severity*

- Afflicts 6 million people in the U.S. and 28 million people globally<sup>1</sup>
- In U.S.: Most frequent cause of hospitalization for people ages 65+<sup>2</sup>
- Mortality in patients with moderately severe symptoms is worse than most cancers: 50% are dead five years after diagnosis<sup>1</sup>
- In 2012, the annual cost of heart failure in the U.S. was \$31 billion, with projections suggesting an increase to \$70 billion by 2030<sup>1</sup>

<sup>1</sup> Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2015 update: a report from the American Heart Association. *Circulation*. 2015;131(4):e29-e322.

<sup>2</sup> Hall MJ, DeFrances CJ, Williams SN, et al. National Hospital Discharge Survey: 2007 summary. National health statistics reports; no 29. Hyattsville, MD: National Center for Health Statistics. 2010.