mesoblast

Newsletter

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Mesoblast's Revascor Shows Great Promise in Meeting the Treatment Gap in Advanced and End-Stage Chronic Heart Failure

What is Heart Failure?

Heart failure is a very serious and progressive condition caused by weakness of heart muscle and is the leading cause of recurrent hospitalizations in people older than 65 in the United States. In the United States alone, there are more than 1.3 million patients with advanced chronic heart failure who have high rates of morbidity and mortality despite maximal existing therapies. This well-defined major treatment gap in these needy patients is a potential multi-billion dollar market opportunity for Mesoblast.

The heart muscle is so badly weakened in patients with heart failure that it is unable to pump an adequate supply of blood around the body, starving the body of sufficient oxygen and nutrients to operate effectively. The most common causes of heart muscle damage are narrowing of the arteries to the heart muscle (called ischemic heart failure due to coronary artery disease), high blood pressure, or damage to the heart muscle due to genetic, infectious or drug-related causes (dilated cardiomyopathy). Each of these initiating factors ultimately results in severe inflammation in the damaged heart which then causes further progression of heart failure.

How does inflammation cause progressive heart failure?

The heart contains certain immune cells called M1 macrophages. In chronic heart failure, these pro-inflammatory M1 macrophages become activated and release certain inflammatory factors, such as TNF-alpha, interleukin-1 and interleukin-6, which directly cause death of heart muscle cells and replacement with scar tissue.

In addition, these inflammatory factors cause constriction of blood vessels and prevent adequate blood flow to the heart and to organs such as skeletal muscles and the kidneys. This is called endothelial dysfunction, and results in worsening ability of the heart to pump, inability to exercise, and kidney failure.

Many commonly used drugs in heart failure work by directly relaxing these abnormal blood vessels and improving blood flow. However, despite maximal standard of care, many patients continue to suffer with progressive heart failure, thus indicating the need for therapies with anti-inflammatory effects and the potential to reverse endothelial dysfunction.

Why is inflammation further aggravated by implantation of a Left Ventricular Assist Device (LVAD) and how does it manifest clinically?

In patients with end-stage heart failure, placement of an LVAD to take over the heart's pump function can be life-saving. However, the LVAD is a foreign object and its implantation results in further increases in M1 macrophages in the heart and blood that results in even higher levels of inflammatory factors in a futile attempt to eliminate the foreign object. The end result is further worsening of endothelial dysfunction and reduced blood flow to organs.

In these patients the endothelial dysfunction and reduced blood flow causes a compensatory abnormal network of blood vessels in the gastrointestinal tract which results in severe and life-threatening bleeding in up to 40 percent of patients with LVADs.

How do Mesoblast's proprietary Mesenchymal Precursor Cells (MPCs) reduce damaging inflammation and reverse endothelial dysfunction?

Mesoblast's preclinical studies have shown that MPCs secrete specific factors which convert the pro-inflammatory M1 macrophage to an anti-inflammatory M2 macrophage (a phenomenon termed macrophage polarization). This results in switching off the production of damaging inflammatory factors.

In large animal studies of systemic inflammation, a single intravenous injection of Mesoblast's MPCs switched off inflammation and reversed endothelial dysfunction in multiple organs including the coronary arteries in the heart. This suggests that macrophage polarization was responsible for both reduction in inflammation and reversal of endothelial dysfunction.

Placing MPCs into inflamed hearts in preclinical large animal models of heart failure has resulted in formation of new blood vessels, reduction in scarring and fibrosis, prevention of cardiac dilatation, and improvement in heart function.

What have we learnt from Mesoblast's Phase 2 trial of its MPC product candidate Revascor in advanced chronic heart failure?

Mesoblast is developing Revascor* to fill the treatment gap for both advanced and end-stage chronic heart failure. Revascor comprises 150 million MPCs. The objective of treatment with Revascor is to use this cellular medicine in patients with advanced and end-stage heart failure who are no longer responsive to maximal standard of care heart failure drugs in order to prevent or delay further progression of heart failure or death.

Mesoblast completed a Phase 2 randomized, placebo-controlled, dose-escalation trial of MPCs in 60 patients with moderate to advanced heart failure. The objectives of this trial were to identify an optimal therapeutic dose and an ideal target patient profile for eliciting a treatment response to Revascor.

The results showed that over three years of follow up, the patients who had been treated with the highest MPC dose of 150 million cells were significantly protected from recurrent hospitalizations from heart failure or death compared to those who received placebo. In addition, the 150 million MPC dose provided the greatest protection against enlargement of the left ventricle and the greatest improvement in exercise capacity. On the basis of these results, the optimal dose for therapeutic benefit was determined to be 150 million MPCs.

In a post-hoc analysis of the Phase 2 data, it was also found that control patients with very enlarged hearts (left ventricular end systolic volume >100ml) deteriorated most rapidly, while similar patients receiving 150 million MPCs were protected against disease progression. These Phase 2 findings identified the patient population most likely to benefit from Revascor and guided the clinical trial design for the subsequent Phase 3 study.

What is the status of the Phase 3 trial of Revascor in advanced chronic heart failure?

Enrollment has just been completed in Mesoblast's placebo-controlled Phase 3 trial of Revascor in 566 patients with moderate to advanced chronic heart failure conducted across 55 centers in North America. The trial will complete when sufficient primary endpoint events have accrued, which is likely to be within 12 months.

Based on the prior Phase 2 experience and the assumptions used in the design of this Phase 3 trial, the Company is confident that the total of 566 randomized patients in the Phase 3 trial will be sufficient to show whether Revascor is superior to placebo in the trial's primary endpoint of reduction in heart failure-related hospital admissions, and in the key secondary endpoint of reduction in cardiac death.

The patients who have been enrolled in the Phase 3 trial have very similar characteristics to those patients with the most severe form of the disease in the prior Phase 2 trial where Revascor showed maximal benefit. In the Phase 3 trial, Revascor was successful in April 2017 in a pre-specified futility analysis of the trial's primary endpoint in the first 270 patients enrolled in the trial.

Mesoblast's cardiovascular partner in China, Tasly Pharmaceutical Group, is planning to meet with the National Medical Products Administration (NMPA) of China, formerly known as the China Food and Drug Administration, in the first quarter of 2019 to discuss the regulatory approval pathway for Revascor in China. The objective is to initiate a Phase 3 trial of Revascor in China using similar clinical endpoints and targeting a similar patient population of advanced heart failure patients at high risk of recurrent heart failure-related hospitalization and death. Tasly and Mesoblast will leverage each other's clinical trial results in China, the United States and other territories to support their respective regulatory submissions.

What is the evidence that Revascor was effective in LVAD patients and what is the likely read-through to the Phase 3 trial?

In the Phase 2 trial of Revascor in 159 patients with end-stage heart failure and an LVAD, a single injection of Revascor directly into the heart resulted in a 76 percent reduction in major GI bleeding events and in a 65 percent reduction in associated hospitalizations. This strongly suggests that Revascor reversed endothelial dysfunction which is responsible for the abnormal vasculature in the GI tract and severe bleeding in LVAD patients.

The patients with ischemic heart failure benefited the most from treatment with Revascor in the Phase 2 LVAD trial. Since these closely resemble the majority of patients enrolled in the ongoing Phase 3 trial of patients with moderate to advanced heart failure, this may have significant read-through to the Phase 3 trial where intra-cardiac inflammation and peripheral vascular dysfunction are thought to directly result in recurrent hospitalizations and death.

Can Mesoblast leverage the observed reduction in GI bleeding in LVAD patients to support a potential early marketing approval for Revascor?

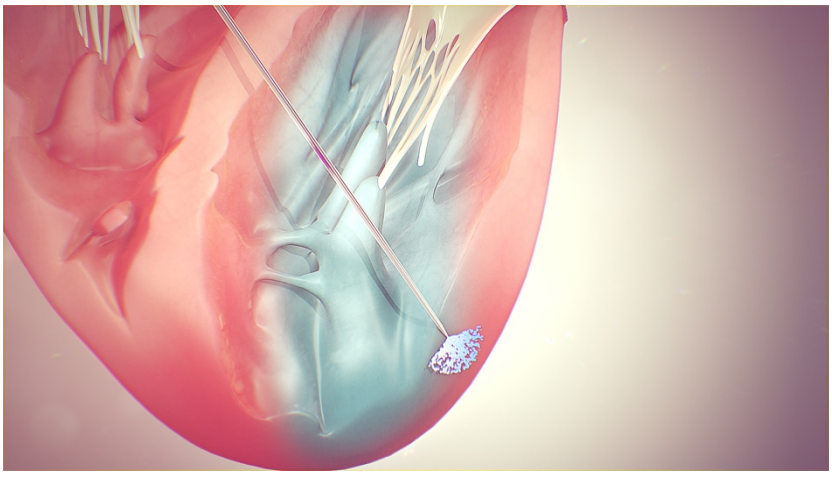
Reduction in GI bleeding and associated hospitalizations in a previous 30-patient pilot trial of Mesoblast's MPCs were the basis of the Regenerative Medicine Advanced Therapy (RMAT) designation granted in December 2017 by the FDA for use of Revascor in LVAD patients.

In a subsequent meeting in 2018, the FDA advised Mesoblast that the defined endpoint of reduction in major GI bleeding and rehospitalization is an appropriate clinically meaningful endpoint and could be the basis of an approved indication for use of Revascor given the life-threatening nature of the condition, and the RMAT designation under which Revascor is being regulated.

In the first half of 2019, Mesoblast plans to meet with the FDA to discuss the pathway for approval of Revascor in end-stage heart failure patients for the reduction in GI bleeding.

The Company intends to seek accelerated approval for direct intra-cardiac injection of Revascor as an adjunct to LVAD implants in end-stage heart failure patients. Should Mesoblast be successful with an early market entry for Revascor then once sufficient Phase 3 clinical evidence has been collected, the Company can apply for an indication extension of the product for treatment of patients with moderate to advanced heart failure to prevent progression to end-stage disease.

**The name Revascor is based on the process of restoring the flow of blood to the heart*



Revascor is delivered directly into the damaged heart.