2. SCIENTIFIC ABSTRACT

This is our third clinical study using our SDF-1 non-viral plasmid DNA therapy to be submitted to the Office of Biotechnology Activities – Recombinant DNA Advisory Committee. Currently, there are two active INDs utilizing exactly the same SDF-1 plasmid DNA drug product and formulation, JVS-100 (formerly called ACRX-100). To date, 17 subjects have been enrolled in a Phase I open label, dose escalation trial examining the safety and efficacy of JVS-100 delivered via an endomyocardial needle injection catheter in subjects with chronic heart failure (IND#14203, RAC#0910-1004) and a 48-subject Phase IIa double blind, randomized, placebo controlled study of JVS-100 to examine safety and efficacy in subjects with critical limb ischemia will begin enrollment in Q3 2011 (IND#14569, RAC#1010-1070). This RAC submission proposes the use of JVS-100 treatment in an additional set of chronic heart failure patients delivered via retrograde infusion.

Heart failure (HF) is one of the leading causes of morbidity and mortality in Westernized countries. Even in the presence of current guideline-based therapy, HF has a US prevalence of 5.4 million and an incidence of 690,000 new cases/year. Through investigations focused on defining the parameters of myocardial stem cell homing, Juventas Therapeutics identified Stromal cell-Derived Factor-1 (SDF-1, a.k.a. CXCL12) as a chemokine that is transiently expressed post-tissue injury to promote tissue repair by preventing cell death and recruiting blood borne and tissue specific stem cells to the damaged region. SDF-1 is a naturally occurring chemokine that is rapidly increased after myocardial infarction for a period of 4-5 days.[1, 2] SDF-1 triggers a number of protective molecular cascades that are both anti-inflammatory[3] and anti-apoptotic to preserve cardiac tissue after injury.[4] Furthermore, SDF-1 is a strong chemoattractant of stem cells and progenitor cells that promote tissue preservation and blood vessel development. The tissue-preserving and reparative effects of SDF-1 identified by Juventas led us to investigate the potential role of SDF-1 in treating ischemic cardiovascular disease. Chronic ischemic damage via MI causes significant loss of cardiac function which often leads to symptomatic heart failure (HF) even when treated with current guideline based medical therapy. Juventas' product, designated JVS-100, is a non-viral SDF-1-encoding plasmid that can be directly delivered to the heart anytime post-MI.

JVS-100 safety and efficacy has been rigorously tested in preclinical models of ischemic heart failure. We delivered multiple injections of JVS-100 at a single time into pigs 30 days following MI with systolic dysfunction (LVEF<40%) and evidence of adverse cardiac remodeling (LVESV>56.7 ml) at one of three total doses ranging in total DNA from 7.5 mg (low), 30 mg (mid) to 100 mg (high) or placebo. All JVS-100 doses demonstrated safety assessed by standard clinical observations, clinical pathology and detailed histopathological analysis. Vessel density was significantly increased in the 7.5 mg and 30 mg dose groups at 30 days compared to control ($P<0.05$). The 7.5 mg and 30 mg dose groups showed a substantial reduction in LVESV at 60 days compared to control, whereas the high dose animals had no functional benefit. Trends in all doses continued to 90 days. This data served as the basis for our ongoing ascending dose Phase I, 17 subject clinical trial (study #JTCS-001, IND#14203, RAC#09101004) in subjects with NYHA Class III heart failure, prior MI and an ejection fraction≤40%.

On December 16, 2010 enrollment in the Phase 1 open label study (n=17 subjects) was completed. Subjects received one of three doses of JVS-100, 5 mg (n=4 pts), 15 mg (n=6 pts), or 30 mg (n=7 pts), delivered to the peri-MI region via 15 endomyocardial injections with the BioCardia Helical Infusion Catheter. The DSMC has evaluated safety data from the first and second cohort and unanimously recommended escalating to Cohort 3 dosing. Follow-up has been completed through 4 months in the 5 and 15 mg cohorts and 1 month in the 30 mg cohort. The drug has been well tolerated to date as 14 Serious Adverse Events (SAEs) have occurred, with only one being possibly related to the drug. The primary safety endpoint, the number of Major Adverse Cardiac Events at 1 month post-injection, has been met, with only 2 MACEs occurring within 30 days of injection, both due to underlying disease. Two subject deaths have occurred, both unrelated to study drug, device or procedure, the other 15 subjects continue in active follow-up. Interim efficacy data available from the low (5 mg) and mid (15 mg) dose

suggests subjects are improving function and overall health status. Both the low and mid dose groups show improvements in 6-minute walk distance (5 mg: 24 m median improvement; 15 mg: 41 m median improvement) and quality of life (5 mg: 12 point median improvement; 15 mg: 16 point median improvement) at 4 months compared to baseline. All clinical data to date suggests JVS-100 is safe to deliver to heart failure subjects at doses up to 30 mg and may provide functional benefit at doses up to 15 mg (30 mg data pending).

In the Phase Ib trial outlined in this submission, we propose to deliver JVS-100 via an alternative delivery system, retrograde infusion, to the same population of chronic heart failure subjects targeted in our current Phase 1 clinical study. Retrograde infusion is defined as percutaneous delivery of liquid treatment (e.g. cells in solution, genes in solution) through the coronary venous system, and has been utilized for years to deliver cardioplegia to subjects undergoing cardiac surgery or high-risk coronary interventions.5-8 We have performed an expression study in a post-MI porcine model where JVS-100 with the SDF-1 gene switched for a reporter gene (luciferase) was delivered via retrograde infusion at either 5 or 15 mg. Expression was assessed at 3 days post-infusion by excising the heart and performing bioluminescence imaging. The 15 mg dose demonstrated significant protein expression. Expression was not detected at a 5 mg dose level. Based on this data, we propose to test delivery of JVS-100 via retrograde infusion at dose levels of 15 and 30 mg in an open-label Phase Ib dose-escalation study.

In brief, subjects on optimal pharmacological therapy with symptomatic (NYHA Class II/III heart failure with 6 minute walk distance ≤400 m), systolic dysfunction (LVEF≤40%), and prior well-demarcated MI will be enrolled. Each subject will receive 40 ml of JVS-100 delivered via retrograde infusion in a coronary vein proximal to the infarct site. Dose will be escalated by increasing the total amount of JVS-100 delivered per patient from 15 mg (n=6 subjects) to 30 mg (n=6 subjects). Subjects will be monitored overnight post-dosing to ensure that there are no safety concerns. Safety endpoints include physical assessment, clinical pathology (cardiac enzymes, and complete blood count), safety echocardiography, ECG, and adverse events. All subjects will have follow-up at 1 month, 4 months, and 12 months to assess safety and cardiac function. The primary safety endpoint of number of major adverse cardiac events (MACE) occurs at the 1 month follow up. Efficacy endpoints will include change in LVESV, NYHA classification, quality of life, six minute walk distance, and perfusion by SPECT imaging. Following the final dosing of the cohort, all safety data collected during the 7 days following each subject's dosing with JVS-100 will be reviewed by the independent medical monitor. The medical monitor must approve escalating to the next dose. Safety oversight will be performed by an independent Data Safety Monitoring Committee (DSMC).