2. SCIENTIFIC ABSTRACT

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 Americans 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 ACRX-100, is a non-viral SDF-1-endoding plasmid that can be directly delivered to the heart anytime post-MI.

The dosing regimen used in all porcine studies was a single dose administration to the heart at multiple injection sites with BioCardia's *Helix* transendocardial delivery catheter system. For the pivotal GLP study, we delivered multiple injections at a single time of ACRX-100 into pigs 30 days following MI with systolic dysfunction (LVEF<40%) and evidence of adverse cardiac remodeling (LVESV>56.7 ml) at three total doses ranging in total DNA from 7.5 mg (low), 30 mg (mid) to 100 mg (high). Animals were sacrificed at either 3, 30, or 90 days, and assessed for safety by standard clinical observations, clinical pathology and detailed histopathological analysis. Histological analysis showed no evidence of toxicity compared to control in any dose delivered. Analysis of the infarct border zone by a pathologist blinded to treatment group indicated that ACRX-100 treated animals in the low and mid dose groups demonstrated evidence of accelerated healing compared to controls at 30 days. Vessel density were significantly increased in the low and mid dose groups at 30 days compared to control ($P<0.05$). The low and mid 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. These findings were consistent with rat HF studies in which we demonstrated ACRX-100 significantly ($p<0.05$) improved fractional shortening and pilot porcine HF studies in which we showed 4 mg of total DNA yielded no functional improvement at 60-days post treatment but that re-dosing these animals with 30 mg total DNA significantly improved LVESV and LVEF at 60 days post-treatment (5 months post-AMI). These data are the basis for a proposed 16 subject Phase I open-label dose escalation clinical trial evaluating safety and preliminary efficacy of ACRX-100 in Class III heart failure patients receiving 5, 15 or 30 mg of therapy.

In brief, subjects on optimal pharmacological therapy with symptomatic (NYHA Class III) heart failure, systolic dysfunction (LVEF<40%), prior well-demarcated MI, and an implanted Automatic Implanted Cardioverter Defibrillator (AICD) will be enrolled. Each subject will receive fifteen (15) 1 ml injections of ACRX-100 delivered by an endocardial needle catheter to sites within the infarct border zone. Dose will be escalated by increasing the total amount of ACRX-100 delivered per patient from 5 mg (low dose, n=4 subjects) to 15 mg (middle dose, n=6 subjects) to 30 mg (high dose, n=6 subjects). Subjects will be monitored overnight post-dosing and have scheduled visits at 3 and 7 days post-injection 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 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 ischemic area by SPECT imaging. Within each cohort, subjectenrollments will be separated by at least 3 days. Following the final dosing of the cohort, all safety data collected during the 14 days following each subject's dosing with ACRX-100 will be reviewed by the Data Safety Monitoring Committee (DSMC). The DSMC must approve escalating to the next dose.