SDF-1 Plasmid Treatment for Patients with Heart Failure (STOP-HF)

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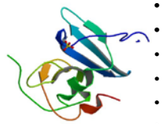
On behalf of the STOP-HF Investigators# & Juventas Therapeutics*, Cleveland, Ohio

Background



SDF-1

- Also known as CXCL12
- 8 kDA chemokine, receptor is CXCR4
- Upregulated in damaged tissue, including skin[4]
- Improves cardiac function after acute myocardial infarction[5]
- Mobilizes/recruits hematopoietic stem cells to injured tissue[1]
- SDF-1 is increased in wounds after trauma[3]
- SDF-1 therapy in diabetic wounds increased healing[2]

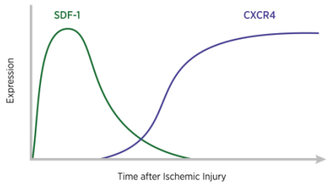


Figure 1. SDF-1 and CXCR4 expression after an ischemic injury.
SDF-1 expression is temporarily increased after an injury but soon fades, whereas the primary SDF-1 receptor, CXCR4, is continually upregulated in ischemically damaged tissue.

Hypothesis:

Re-introducing SDF-1 expression in a chronically damaged heart using plasmid DNA may increase cardiac function.

Phase I Results

NYHA Improvements (Cohorts 2 & 3)

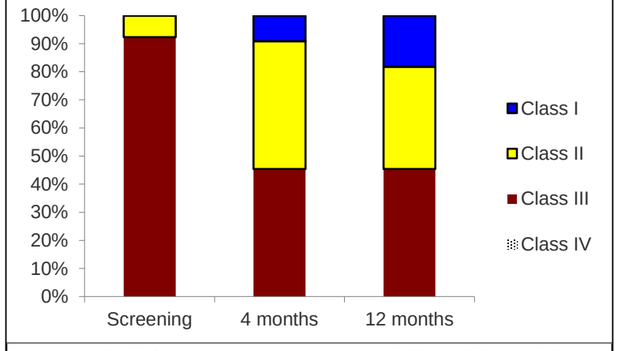


Figure 4. JVS-100 demonstrates improvement in NYHA Class in Cohorts 2 & 3.
Improvement in the 15 and 30 mg combined groups was statistically significant as compared to baseline ($p<0.05$). At 12 months, in the 15 and 30 mg dose groups, improvements (60% and 50% improved at least 1 heart class, respectively) were maintained.

Phase I Results

JVS-100 Exhibits Improvements in QoL through 12 Months

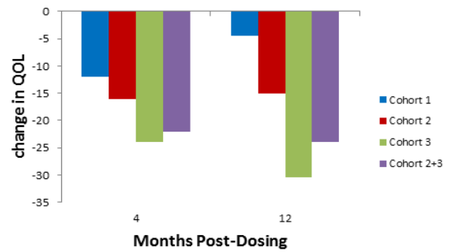


Figure 2. JVS-100 exhibits improvement in MLWHFQ scores at 4 and 12 months
At 4 months, there was a dose-dependent improvement in QOL in all groups. At 12 months, the 15+30 mg group improved QOL (Median[Range]: -24 points[-56 to 7], $p<0.01$), as compared to the 5 mg group (Median QOL: -5 points).

JVS-100 Shows Improvement in 6MWD at 4 and 12 Months

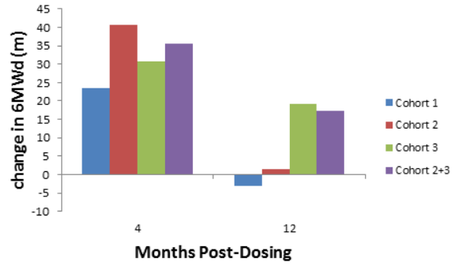
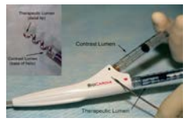


Figure 3. JVS-100 shows improvement in 6MWD at 4 and 12 months.
Improvement in the 15 and 30 mg dose groups combined was statistically significant over baseline (median 36 m, $p=0.002$). At 12 months, there was a reversion to baseline values in the 5 and 15 mg dose groups, but maintained improvement in the 30 mg dose group.

Phase I Adverse Event Summary

- Overall, JVS-100 was safe and well-tolerated.
- 26 SAEs were reported in subjects that received study drug. Only 1 SAE (worsening heart failure) was thought to be "possibly" related to JVS-100. No other subjects had any serious adverse events reported as "related" or "possibly related" to JVS-100.

Phase II Trial Design



Phase II randomized, placebo controlled, double-blind study is being conducted at 16 participating centers. Study design is described in Table 1. All patients have an EF <40%. All patients are dosed on day 0 with 15 1 ml injections using the BioCardia helical infusion system. Safety is assessed at 3 days, 1, 4 and 12 months post-injection, with efficacy also assessed at 4 and 12 months.

Trial Design:

- 90 Person randomized, double blind, placebo controlled trial
- 6MWD<400 m, MLWHFQ score > 20
- EF < 40%
- 3 Cohorts (1:1:1): Placebo; 15 mg; 30 mg
- 12 month follow-up
- Delivered via direct LV intramyocardial injection using the BioCardia Helical Infusion system
- 15 injections of 1 ml for each patient

Endpoints:

- **Primary:** Change in 6MWD at 4 months, change in MLWHFQ score at 4 months
- **Secondary:** NYHA class, functional echo parameters at 4 and 12 months, 6MWD, MLWHFQ at 12 months, additional mortality and morbidity endpoints

Patient Profile	
Age (yr)	66.0 ±9.0
Time since last MI (yr)	11.1±9.9
Gender (% Male)	87%
NYHA Class III	65%
6 Min. Walk (m)	295±89
QoL Score	49±19
LVESV (ml)	109±35
LVEF (%)	28±6.4
Ischemic CM (%)	100%

Major Inclusion/Exclusion

Major Inclusion Criteria:

- Symptomatic Ischemic Cardiomyopathy
  - MI at least 6 months ago
  - EF<40%, 3 contiguous LV segments w/ abnormal WMSI
- Functional ICD
- Minnesota Living with Heart Failure Questionnaire score > 20
- 6 Minute Walk Distance < 400 m
- Optimal Pharmacological Therapy
  - Beta blockers
  - Diuretics
  - ACE Inhibitors and/or ARB
  - Statin unless contraindicated

Major Exclusion Criteria:

- Active cancer other than non-melanoma skin cancer
- Artificial aortic valve
- Scheduled for revascularization in next 30 days
- Scheduled for mitral valve repair or replacement
- BiV pacemaker or ICD implanted or re-optimized in the last 90 days

Centers Participating

- Cardiology PC (Birmingham, AL)
- Columbia University Medical Center (New York, NY)
- Minneapolis Heart Institute Foundation (Minneapolis, MN)
- University of Utah (Salt Lake City, UT)
- The Lindner Center for Research (Cincinnati, OH)
- Pepin Heart Institute (Tampa, FL)
- Montefiore Medical Center (Bronx, NY)
- SUMMA Health System (Akron, OH)
- University of Pennsylvania (Philadelphia, PA)
- University of Florida (Gainesville, FL)
- Michigan Cardiovascular Institute (Saginaw, MI)
- Baylor Health (Dallas, TX)
- Johns Hopkins University (Baltimore, MD)
- Spectrum Health (Grand Rapids, MI)
- Iowa Heart Center (Des Moines, IA)
- Washington University in St. Louis (St. Louis, MO)

Recruitment Dates

The study began enrolling in August 2012 and will end recruitment in October 2013

Inquiries on Future Trials

Contact the sponsor, Juventas Therapeutics, by emailing Joseph Pastore (jpastore@juventasinc.com) or Scott Fisher (sfisher@juventasinc.com). While the sites have already all been selected for the Phase II study, Juventas will be considering a number of new sites for anticipated future studies. Information to include/consider:

- Experience with cardiovascular and/or gene therapy trials
- Historical recruitment rates for similar trials
- Strength of relationship between interventional cardiology and heart failure research programs at your site
- Advanced echocardiography capabilities