An Open Label Dose Escalation Study to Evaluate the Safety of Administration of Non-viral SDF-1 Plasmid to Treat Symptomatic Ischemic Heart Failure

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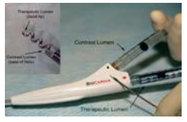
Abstract

JVS-100 comprises a non-viral DNA plasmid engineered to transiently express human Stromal-cell Derived Factor 1 (**SDF-1**). SDF-1 triggers a number of protective molecular cascades that are both anti-inflammatory and anti-apoptotic. Furthermore, **SDF-1** is a strong chemoattractant of stem cells and progenitor cells that promote tissue preservation and blood vessel development. Previous studies have demonstrated that **SDF-1** expression is increased in the myocardium after a myocardial infarction, but expression lasts for less than a week, and therefore the induced stem cell homing response quickly fades. This short duration of **SDF-1** expression reduces the potential for tissue repair and suggests that therapeutic interventions which prolong the ability of **SDF-1** to stimulate the stem cell homing process may be beneficial for patients that have damaged heart tissue. A 57-pig safety and efficacy study evaluated cardiac functional response, toxicity and bio-distribution in a porcine model of heart failure after treatment with escalating doses of JVS-100. At 60 days post-therapy, JVS-100 improved LVEF and LVESV at low and mid doses. JVS-100 promoted vasculogenesis at all doses relative to controls, with significant increases at the low and mid doses at 30 days post-injection. Based on these results, the FDA allowed an IND to initiate an open label, 17 subject Phase 1 dose-escalation study. 17 patients with chronic NYHA class III ischemic heart failure (HF) and ejection fraction ≤ 40% received JVS-100: 5 mg (n=4), 15 mg (n=6) and 30 mg (n=7) delivered via 15 endomyocardial injections with the BioCardia Helical Infusion Catheter and followed at 1, 4, and 12 months. Based on the preclinical results, it was pre-specified that the 15 and 30 mg dose groups would be combined. Efficacy assessment included changes from baseline in: echocardiographic/SPECT parameters, NYHA class, 6 minute walk distance (6MWd) and quality of life score (QOL). At 4 months, there was a dose-dependent improvement in 6MWd and QOL in all groups. At 12 months, the 15+30 mg group improved QOL (Median[Range]: -24 points[-56 to 7], p<0.01), 6MWd (Median[Range]: 17 m[-96 to 112]) compared to the 5 mg group (Median 6MWd: -3 m, Median QOL: -5 points). SPECT imaging showed that the summed difference score, a marker of reversible ischemia, had a significantly (p<0.01) higher increase (median: 8.5 points) in the 5 mg group at 4 months versus the 15+30 mg group (median: 0 points). These Phase 1 data suggest that re-establishing SDF-1 expression through delivery of JVS-100 to patients with severe chronic heart failure provide sustained, clinically-significant improvements in 6MWd and QOL through 12 months. These results will be further tested in a randomized, placebo-controlled Phase II trial.

Methods

Plasmid DNA for all pre-clinical studies was manufactured by **Aldevron LLC** (North Dakota)
SDF-1 ELISA was performed using the R&D Systems (Minneapolis, MN) SDF1 ELISA kit.
MSC transwell migration assay was performed using p12 rat MSCs incubated on 12 uM fibronectin coated transwells. HEK 293 cells were plated in the bottom well and transfected with JVS-100 using Fugene. Migration was assessed over a 4 hour period 3 days post-transfection.



Phase I Dose-Escalation Study was conducted at 4 participating centers. Study design is described in Table 1. All patients were NYHA Class III (n=16) or Class II (n=1) at time of enrollment. All patients had an EF <40%. All patients were dosed on day 0 with 15 1 ml injections using the BioCardia helical infusion system. Safety was assessed at 3 days, 7 days, 1, 4 and 12 months post-injection, with efficacy also assessed at 4 and 12 months.

Trial Design:

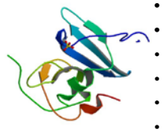
- 17-Person, open-label dose escalation trial
- Class III HF
- EF < 40%
- 3 Cohorts: 5 mg (n=4); 15 mg (n=6); 30 mg (n=7)
- 12 month follow-up
- Delivered via direct LV intramyocardial injection using the BioCardia Helical Infusion system
- 15 injections of 1 ml for each patient

Endpoints:

- **Primary:** Major adverse cardiac events (MACE) at 1 month
- **Secondary:** Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score, NYHA class, 6 minute walk distance (6MWD), SPECT and functional echo parameters at 4 and 12 months

Patient profile	
Age (yr)	65.8±8.5
Time since last MI (yr)	7.3±6.8
Gender (% Male)	71%
NYHA Class III	94%
6 Min. Walk (m)	290±91
QoL Score	54.4±20.5
LVESV (ml)	109±35
LVEF (%)	32.5±5.5
Ischemic CM (%)	100%

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]

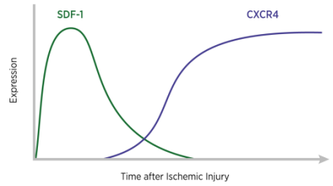


Figure 1. SDF-1 and CXCR4 expression after an ischemic injury.
SDF-1 expression is temporarily increased after an injury but soon fades, whereas the primary SDF-1 receptor, CXCR4, is continually upregulated in ischemically damaged tissue.

Hypothesis:

Re-introducing SDF-1 expression in a chronically damaged heart using naked plasmid DNA gene transfer will increase cardiac function.

Results

JVS-100 Promotes Improvements in QoL through 12 Months

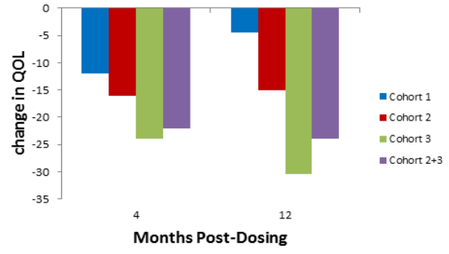


Figure 2. JVS-100 causes improvement in MLWHFQ scores at 4 and 12 months
At 4 months, there was a dose-dependent improvement in QOL in all groups. At 12 months, the 15+30 mg group improved QOL (Median[Range]: -24 points[-56 to 7], p<0.01), compared to the 5 mg group (Median QOL: -5 points).

Results

JVS-100 Improves 6MWD at 4 and 12 Months

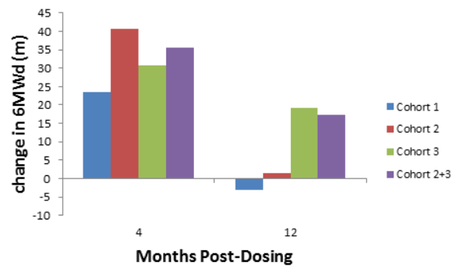


Figure 3. JVS-100 causes improvement in 6MWD at 4 and 12 months.
Improvement in the 15 and 30 mg dose groups combined was statistically significant over baseline (median 36 m, p=0.002). At 12 months, there was a reversion to baseline values in the 5 and 15 mg dose groups, but maintained improvement in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

NYHA Improvements (Cohorts 2 & 3)

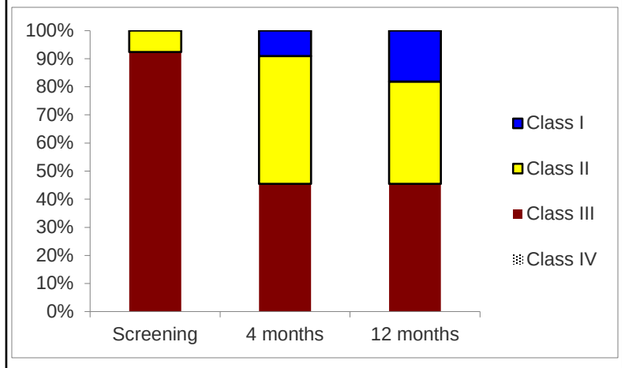


Figure 4. JVS-100 improves NYHA Class in Cohorts 2 & 3.
Improvement in the 15 and 30 mg groups combined was statistically significant over baseline (p<0.05). At 12 months, in the 15 and 30 mg dose groups, improvements (60% and 50% improved at least 1 heart class, respectively) were maintained.

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.

Results

SDS as Measured by SPECT

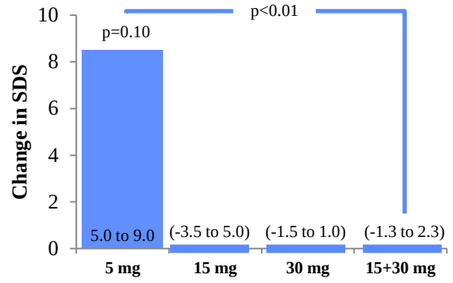


Figure 5. JVS-100 causes stabilization of SDS.
There was an increase in SDS from baseline to 4 months in the 5 mg group. When the change in SDS in the 5 mg group was compared to the combined 15 and 30 mg group, the difference was statistically significant.

Adverse Event Summary Ctd.

- One patient experienced ventricular tachycardia that was reported as "possibly related" to study drug. This event was not serious.
- One subject was diagnosed with systemic lupus erythematosus 16 days after receiving the study drug, however analysis of stored blood samples revealed that the subject had a positive ANA titer (1:320) with positive at baseline, but no history of SLE.
- All subjects experienced a short-term elevation in cardiac enzymes 6-18 hours after the injection. There were no associated cardiac symptoms reported with these enzyme changes.

Summary and Conclusions

Key safety and efficacy findings of the Phase I Dose-Escalation Study:

- JVS-100 was safe and well-tolerated at all doses studied and the primary safety endpoint was met with no adverse events likely related to the drug.
- Injection of 15 and 30 mg doses of JVS-100 improved QOL, 6MWD, and NYHA at 4 and 12 months in NYHA Class III heart failure patients.
- These data served as the basis for a randomized, placebo-controlled 90 patient, Phase II trial (STOP-HF, NCT #01643590) at 12 US clinical sites. In STOP-HF, symptomatic ischemic HF patients are randomized to placebo, 15 mg JVS-100, or 30 mg JVS-100 and the safety and efficacy of JVS-100 will be tested.

References:
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