

2. SCIENTIFIC ABSTRACT

JVS-100 is a non-viral plasmid DNA therapy intended to express Stromal cell-Derived Factor-1 (SDF-1, a.k.a. CXCL12) expression in target tissues and promote healing. The proposed clinical trial of JVS-100 in patients undergoing abdominal scar revision surgery is the **sixth** clinical study to be submitted to the Office of Biotechnology Activities – Recombinant DNA Advisory Committee (RAC). Currently, there are three active INDs utilizing the identical SDF-1 plasmid DNA drug product and formulation of JVS-100 (formerly called ACRX-100). The five clinical protocols previously submitted to the RAC are listed below:

- 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) – 17 subjects enrolled, trial is completed.
- A 48-subject Phase II double blind, randomized, placebo controlled study of JVS-100 to examine safety and efficacy in subjects with critical limb ischemia (IND#14569, RAC#1010-1070) – 46 subjects enrolled.
- A 12-subject Phase Ib open label dose escalation trial examining safety and efficacy of JVS-100 delivered by retrograde infusion in subjects with chronic heart failure (IND#14203, RAC#1103-1098)
- A 90-subject Phase II 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 #14,203; RAC #1201-1140) – 58 subjects enrolled.
- A 25-subject Phase I double blind, randomized, placebo controlled study of JVS-100 to examine safety and efficacy in subjects receiving surgical sternotomy incisions that began enrollment in Q4 2012 (IND #15,053; RAC #1110-1131) – 13 subjects enrolled.

This RAC submission proposes the use of JVS-100 treatment in patients receiving abdominal scar revision surgery via direct needle-free subcutaneous injection to accelerate surgical wound healing and prevent scar formation in patients proven to form hypertrophic scars.

SironRX's drug candidate, designated JVS-100, is a non-viral SDF-1-encoding plasmid that is intended to be directly delivered by topical needle-free injection for the treatment of surgical wounds to accelerate healing and prevent scar formation. Injection of JVS-100 results in expression of Stromal cell-Derived Factor-1 (SDF-1, a.k.a. CXCL12) in target tissues. SDF-1 is a chemokine that is transiently expressed post-tissue injury to promote tissue repair by preventing cell death and recruiting bloodborne and tissue specific stem cells to the damaged region. SDF-1 is a naturally occurring chemokine that is rapidly increased after tissue injury for a period of 4-5 days.^{1, 2} SDF-1 triggers a number of protective molecular cascades that are both anti-inflammatory³ and anti-apoptotic to preserve 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 led us to investigate the potential role of SDF-1 in accelerating wound repair and prevention of scarring.

JVS-100 safety and efficacy has been rigorously tested in multiple preclinical animal models of wound healing, scar reduction, heart failure, and critical limb ischemia. We have previously demonstrated that treatment of full thickness incisional or excisional wounds with SDF-1 accelerated healing and decreased scar formation compared to controls.⁵ Additional preclinical studies evaluated the safety and efficacy of JVS-100 in full thickness porcine wounds after subcutaneous administration by the Biojector 2000. The Biojector 2000 is an FDA-cleared device for subcutaneous and intramuscular delivery and has delivered over 20 million human injections.^{6, 7} We have demonstrated that subcutaneous injection of JVS-100 vector with a reporter gene delivered with the Biojector 2000 results in significant injection site-specific expression 3 days post-injection in pigs. Furthermore, we demonstrated that JVS-100, delivered as injections spaced every 1.25 or 2.5 cm, enhanced healing of surgical wounds over 90 days and

decreased scar formation compared to controls. All JVS-100 doses delivered in animals up to 100 mg have demonstrated safety assessed by standard clinical observations, clinical pathology and detailed histopathology analysis.

Clinically, JVS-100 has been safely administered to more than 100 subjects across 4 phase I and II clinical trials, with no serious adverse events related to study drug. The clinical data suggest that re-establishment of SDF-1 expression through the endomyocardial delivery of non-viral plasmid JVS-100 to subjects with severe chronic heart failure is safe.⁸ All clinical data to date suggests JVS-100 is safe to deliver at doses up to 30 mg and may provide functional benefit at doses up to 30 mg.

In a Phase I wound healing and scar prevention clinical trial, JVS-100 has been delivered via needle-free subcutaneous injection in subjects receiving a median sternotomy during cardiovascular surgery. In brief, 24 subjects between 40-80 years of age receiving a median sternotomy of 16-25 cm in the process of cardiothoracic surgery are being enrolled consecutively and followed for 6 months post-dosing. Three cohorts of 8 subjects each are randomized 3:1 to receive a single set of needle-free subcutaneous injections of either JVS-100 or vehicle control. JVS-100 or vehicle is delivered along the edge of the sternal wound with the Biojector 2000, a needle-free injection device with FDA-clearance for subcutaneous injections. The number of injections per wound segment length is held constant and dose escalation occurs by increasing JVS-100 concentration from 1 mg/mL (Cohort 1), to 2.0 mg/mL (Cohort 2), or by doubling the number of injections at 2.0 mg/mL (Cohort 3). Depending on the length of the subject's sternal wound, subjects in Cohort 1 received 3.5 - 5 mg, subjects in Cohort 2 will receive 7 - 10 mg, and subjects in Cohort 3 will receive 13 - 20 mg JVS-100. Safety and efficacy endpoints are collected over 6 months. As of July 15, 9 subjects were enrolled in Cohort 1 and 4 subjects have been enrolled in Cohort 2. No serious adverse events likely related to drug have been reported for any of the dosed patients.

Using a design similar to the Phase I study described above, the proposed Phase II study will enroll sixty (60) subjects (3 sequential cohorts of 20 subjects each) receiving surgical incisions during abdominal scar revision surgery. Subjects will be enrolled consecutively. Within each cohort, subjects will be randomized 3:1 to receive either JVS-100 or placebo administered via the Biojector 2000, an FDA-cleared device for needle-free dermal injections of drug. The injections will be administered at preset intervals on each side of the incision within 45 minutes of closure at the end of surgery. Subjects will be monitored per protocol for 6 months post-dosing for safety and efficacy endpoints. Prior to enrollment, all subjects must grant written informed consent to participate in the study. Subjects will be screened (CBC, PT/PTT/INR, HgbA1c, and ANA) for study eligibility within 4 weeks prior to planned surgery.

Each subject will be randomized the day prior to surgery and the clinical center notified of the randomization prior to the injection procedure. The subject will be considered enrolled when he or she receives study drug or placebo after wound closure. All subjects will have a single procedure and follow-up monitoring at the day of hospital discharge, 3 weeks, 6 weeks, 3 months, and 6 months post-dose to assess safety and efficacy. After the final dosing of the last subject in each cohort, prior to dose escalation, all safety data reported during the 7 days following each subject's dosing with JVS-100 will be reviewed by an independent Data Safety Monitoring Committee (DSMC) before escalation to the next dose. An independent Data Safety Monitoring Committee (DSMC) will be responsible for safety oversight, adjudication of adverse events, and review of any subject data that meets stopping rules.