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(date) September 6, 2013

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Commercialization of a Novel Wound Therapy and Scar Prevention Product

Abstract

by

MICHAEL RYAN HALLEN

There is an unmet need for more rapid dermal wound healing and scar prevention, both domestically and internationally. SironRX Therapeutics, a startup company spun-out from Juventas Therapeutics and Cleveland Clinic, is undergoing clinical investigations of its lead product, JVS-100. This novel technology encodes a powerful protein, SDF-1, and allows SironRX to approach wound healing and scar prevention in a unique way – by exploiting the body's own regenerative capabilities, creating an advantage over competitors. If proven safe and effective in clinical trials, JVS-100 could have a major impact on the wound healing market. After completion of Phase I clinical trials and demonstration of the safety of its novel therapy, SironRX will face certain decisions including design of late stage clinical trials, financing, and exit strategies. This thesis analyzes SironRX and determines how it can successfully commercialize its product and become a strong competitor in the wound healing market.

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Introduction

SironRX Therapeutics, spun out from Juventas Therapeutics in December 2010, is progressing through a Phase I clinical trial to test the safety and efficacy of its lead technology, JVS-100.¹ This novel therapy exploits a naturally occurring process in which a protein, stromal cell-derived factor-1 (SDF-1), signals the homing of stem cells to an injury site after tissue damage.² In 2003, Dr. Marc Penn, the Director of Research at Summa Cardiovascular Institute³ and former cardiologist at Cleveland Clinic, reported the mechanism behind SDF-1.⁴ Evolved by SironRX, this technology has an opportunity to reach widespread use after demonstration of its efficacy in late stage clinical trials. This thesis serves as an analysis of SironRX to date and a review of the necessary steps and options available to SironRX to reach commercialization and sales. Additionally, this thesis will determine the course of action SironRX should take that, if followed, will be the most effective way to bring its technology to market and become a competitor in the wound healing and scar therapy market.

1. Value Proposition

The value proposition of SironRX can be built through an assessment of the needs, approach, benefits per costs, and competition related to the Company and its technology. Based upon this evaluation tool, SironRX has a strong value proposition that it can offer to both physicians and patients interested in improved wound healing and scar prevention. How well a company adds or creates value for its customers determines, in part, the commercialization potential of its product.
1.1 Need

JVS-100 addresses two needs: wound healing and scar prevention. Wound healing can be categorized into two types – acute wounds and chronic wounds. It is necessary to understand the difference between the two types of wounds to gain a better understanding of the market available to SironRX.

1.1.1 Acute Wounds

Acute wounds progress through specific stages and heal in a timely manner. Figure 1 below outlines the progression of acute wounds from the first stage of wound healing to a fully healed wound. Hemostasis, the first stage in wound healing, involves the constriction of vasculature and the formation of clots, resulting in the arrest of blood flow from the wound.\(^5\,^6\) This initial stage of wound healing begins immediately after injury and can last for approximately 15 minutes.\(^7\) Next, inflammation occurs and is characterized by the presence of neutrophils that help clear the wound area of bacteria and dead cells.\(^8\) Macrophages work to bring additional cells, such as keratinocytes and fibroblasts, to the wound site.\(^9\,^{10}\) This process can last for approximately six days.\(^11\)

During proliferation, the third stage of healing, fibroblasts migrate to synthesize collagen and help build the extracellular matrix (ECM), while working with endothelial cells to create granulation tissue, a process that usually begins the third day after tissue injury and lasts for about two weeks.\(^12\) Finally, remodeling serves to physically close the wound.\(^13\) During this stage, the ECM returns to a state resembling undamaged tissue and capillary formation ceases, a process that can take years to complete.\(^14\) At this stage, scars also develop from those that are unpronounced (fine line), to those that are moderately
pronounced (hypertrophic) to those that are largely pronounced (keloid). Many factors play numerous roles, and chemoattraction is abundant, during the wound healing process.

**Figure 1**: Normal wound healing cycle.

There are different types of acute wounds, categorized by the mode of injury and disruption of the skin. These include burns, punctures, abrasions, significant tissue loss, and incisions. Surgery necessitating incisions are common in hospitals and medical facilities. Annually, there are about 50 million inpatient surgical procedures and 35 million outpatient surgery visits in the U.S. While these estimations do not exactly correlate to the number of procedures requiring dermal incisions, the numbers do help to illustrate the need for therapies that help to heal incisional wounds.

Following an incision, it is possible for the wound to become infected, termed a surgical site infection, or SSI, occurring at a rate of 1-3% of patients undergoing surgery. This can have major economic implications for hospitals. In patients undergoing coronary artery bypass grafting, a type of open-heart surgery, the average cost was about $32,000 higher for cases in which a serious SSI occurred, compared to cases in which no SSI occurred. In the U.S., the costs associated with SSIs are thought to be around $3.5 to $10 billion a year. If a wound therapy can speed the rate of healing and prevent an infection from occurring, hospitals and patients would realize a major reduction in costs.
1.1.2 Chronic Wounds

In contrast to acute wounds, chronic wounds are characterized by their inability to heal properly.\textsuperscript{25} Chronic wounds include diabetic foot ulcers, venous stasis ulcers, pressure ulcers (bedsores), and arterial ulcers.\textsuperscript{26} While there is a need for improved treatments in the chronic wound care market, this space is a Red Ocean, where many companies compete in a crowded industry and perpetuate the trade-off between value and cost.\textsuperscript{27} Many of the competitors in the chronic wound market are established corporations, including Johnson & Johnson, Covidien, Kinetic Concepts, and Smith & Nephew.\textsuperscript{28,29}

1.1.3 Factors Affecting Normal Wound Healing

Normal wound healing can be compromised by a number of factors, including obesity, diabetes, ages, and stress.\textsuperscript{30} Patients affected by one or more of these conditions will experience slower wound healing compared to healthier patients. Age is a concern, as the fastest growing age group is comprised of people 60 and older.\textsuperscript{31} Stress is commonplace and interferes with the immune response, delaying wound healing.\textsuperscript{32} Diabetic patients have slow healing wounds, attributable to a number of factors. Some of these factors include prolonged hypoxia, keratinocyte and fibroblast dysfunctions, and decreased angiogenesis, an effect potentially caused by a decrease in stem cell homing.\textsuperscript{33} Finally, about 30\% of adults in the United States are obese, a condition that creates a higher risk of SSIs.\textsuperscript{34} A technology that improves wound healing would be of great benefit to individuals who normally experience delayed wound healing, a population that continues to grow.\textsuperscript{35}
1.1.4 Scar Prevention

A major disadvantage of current scar treatments lies in their approach to reducing the appearance of scars because these therapies attempt to treat the scar after it is formed. Currently, doctors and patients do not have access to prophylactic treatments to prevent the formation of scars. Moreover, current treatments are not extremely effective and cause adverse effects. These therapies can also be very costly to patients, as seen in Table 1 below, and necessitate the need for a more cost-effective treatment that can be used to prevent a scar from forming. The estimated market for a dermal anti-scarring drug is $12 billion.

Table 1: Common treatments for scar revision

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Price</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scar Revision Therapy</td>
<td>&gt;$1,000</td>
<td>45-100% recurrence rate in keloids</td>
</tr>
<tr>
<td>Laser therapy</td>
<td>$350-$500</td>
<td>High recurrence rates</td>
</tr>
<tr>
<td>Cryosurgery</td>
<td>$175 per scar</td>
<td>Causes blistering; painful; limited to small scars</td>
</tr>
<tr>
<td>Steroid Injections</td>
<td>$150 per injection, per scar</td>
<td>Skin and subcutaneous fat atrophy</td>
</tr>
<tr>
<td>Silicone gel sheeting</td>
<td>~$30 per pair</td>
<td>No effect on mature scars</td>
</tr>
</tbody>
</table>

Surgery frequently results in scarring, as it is estimated that 100 million people acquire scars from surgery in the developed world each year. As a result of surgical incisions, raised scars called hypertrophic scars may form, especially in areas where there is tension in the skin. The incidence of hypertrophic scarring after surgery is reported to be 40% to 70%. More aggressive scars called keloids can also form that extend beyond the border of the initial wound. Keloids are very difficult to manage, as they usually recur after removal. Both hypertrophic scars and keloids also have physical effects including pain, itching, and loss of normal function of the affected area.
In addition to the physical consequences and economic costs of treating scars, there are severe emotional consequences and negative effects on quality of life when faced with such disfigurements. In a study of 34 patients with various types of skin scars, more than half of the subjects reported a decline in their relationships with family and friends due to their scars.\textsuperscript{54} The effects on the subjects’ self-confidence extended from social situations to their professional lives in which one-third of subjects stated their scars interfered with their careers.\textsuperscript{55} Figure 2 below summarizes the results from the study, highlighting the major facets of the subjects’ lives that were majorly impacted by their scars.

\textbf{Figure 2:} Effects of scars on quality of life.\textsuperscript{56}

By focusing on acute wounds \textit{and} scar prevention, SironRX is able to take advantage of a Blue Ocean, an uncontested market space, allowing the Company to create value for its customers at a relatively low cost.\textsuperscript{57}
1.1.5 JTBD

The wound healing and scar treatment markets have multiple customer segments. Physicians, patients, and hospital administrators are all involved in the purchasing decision. Among these customers is a unifying job-to-be-done (JTBD): Close skin wounds, e.g. incisional wounds and other acute wounds.

In response to this JTBD, key outcome expectations include:

1. Minimize the amount of scarring after surgery, e.g. size, color, and thickness of scars.
2. Minimize the time it takes to close the wound, e.g. wound follows normal healing cycle.
3. Minimize the likelihood of a wound opening after surgery, e.g. wound does not become infected or develop into a chronic wound.
4. Minimize the cost of reducing scar formation, e.g. one-time prevention therapy.
5. Minimize the cost of healing a wound, e.g. minimal personnel and resources required to close a wound after surgery.

1.2 Approach

SironRX approaches the unmet need for faster wound healing and reduced scar formation using regenerative medicine. Using the body’s natural healing process, SironRX has begun to demonstrate the effectiveness of its lead product, JVS-100, on dermal wounds. JVS-100 is a non-viral DNA plasmid that codes for SDF-1. SDF-1 is a protein, specifically a chemokine, involved in stem cell migration. SDF-1 and its receptor,
CXCL chemokine receptor 4 (CXCR4) are involved in the homing and migration of stem cells from bone marrow.

When tissue becomes damaged, as in the instance of a dermal wound, it becomes hypoxic, or deprived of oxygen. The damaged, hypoxic tissue expresses SDF-1 in abundance and causes a surge of stem cells to navigate from bone marrow to the site of injury. SDF-1 is the ligand to CXCR4, a protein expressed on the surface of mesenchymal stem cells (MSCs). Therefore, tissue repair is stimulated by SDF-1 through the activity of stem cells. It is the regenerative nature of stem cells that serves as the underlying mechanism behind JVS-100.

1.2.1 Stem Cells

Stem cells are undifferentiated cells that are able to continuously self-replicate and have the potential to differentiate into an array of specific cell types. Found throughout the body in different tissue types and organs, stem cells are responsible for repairing damaged tissue, among many other functions. Concerning wound healing, there are many types of progenitor cells involved, two of the most important types of stem cells involved in this process are found in bone marrow hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). Both these cell types have been shown to be involved in wound healing. HSCs differentiate into all types of blood cells and are thought to give rise to endothelial progenitor cells (EPCs), which promote neovascularization and angiogenesis through paracrine signaling. This formation of vasculature is necessary for proper wound healing to occur. MSCs differentiate into various cell types including
osteocytes, chondrocytes, and connective tissue cells. In addition to their multipotency, MSCs are involved in tissue repair.

1.2.1.1 Stem Cells in Wound Healing

MSCs play a role in the different stages of wound healing – inflammation, proliferation, and remodeling. To help decrease inflammation, stem cells inhibit proinflammatory molecules like tumor necrosis factor- \( \alpha \) (TNF- \( \alpha \)) and interferon- \( \gamma \) (INF- \( \gamma \)), while promoting anti-inflammatory molecules like interleukin-10 (IL-10) and interleukin-4 (IL-4), all of which are cytokines, or cell signaling molecules.

MSCs aid in the proliferation stage of wound healing by producing and secreting molecules involved in repairing damaged tissue, like vascular endothelial growth factor (VEGF), which aids in angiogenesis. A well-vascularized tissue is necessary for cells to receive nutrients and for proper wound closure. Other factors include platelet-derived growth factor (PDGF) and epidermal growth factor (EGF). Proliferation is stimulated further when MSCs recruit cells like keratinocytes and fibroblasts to the site of injury.

Remodeling, the final and longest stage of wound healing, involves the accumulation of collagen and a decrease in activity of metalloproteinases. These processes are influenced by MSCs, which have been shown to increase the secretion of collagen from dermal fibroblasts and regulate tissue inhibitor of metalloproteinases (TIMP). Other molecules, like transforming growth factor-beta 3 (TGF-\( \beta \)3), are produced by MSCs, a
necessary step for the final stage of wound healing.\textsuperscript{81}

Based on the powerful nature of stem cells, some may ask why not just transplant MSCs to damaged tissue to aid in wound healing? The answer lies in the fact that MSCs die shortly after being transplanted due to the hypoxic nature of the wounded tissue and lack of nutrients.\textsuperscript{82,83} To overcome this obstacle, steps are being taken to formulate an effective engraftment scaffold to ensure MSCs survive long enough to be incorporated into the wound.\textsuperscript{84} However, SironRX bypasses this hurdle and uses SDF-1 to home MSCs to wounded tissue, so engraftment is not an issue.

1.2.2 Other Effects of SDF-1

SDF-1 has been shown to prevent apoptosis of MSCs.\textsuperscript{85} Although the mechanism behind this finding is not well understood, some have pointed to signaling pathways and the upregulation of anti-apoptotic proteins and downregulation of pro-apoptotic proteins.\textsuperscript{86} Additionally, SDF-1 has been shown to reduce inflammation by acting upstream of the stem cell signaling and results in the anti-inflammatory cascade as mentioned earlier. The benefit of using SDF-1 is that it appears very early in the wound-healing pathway, so one molecule ends up triggering many downstream signaling cascades.\textsuperscript{87}

It is clear that SDF-1 plays a crucial role in repairing damaged tissue; however, its expression is temporary, being at its peak within a few hours of appearance and exponentially decaying in under one week.\textsuperscript{88} Through use of JVS-100, SironRX is able to prolong this transient expression by increasing the levels of SDF-1 protein, resulting in
the extended signaling of stem cells to the site of injury and, therefore, their reparative actions. As such, the protein may be present for multiple weeks rather than for multiple days.\textsuperscript{89} This is believed to enable rapid tissue healing and reduced scar formation.

### 1.2.3 Patents/Licenses

Dr. Marc Penn, while a physician at Cleveland Clinic, discovered the technology used by SironRX. While SironRX does have its own patents regarding aspects of the technology, the original invention was assigned to Cleveland Clinic.\textsuperscript{90} Intellectual property (IP) surrounding this technology was licensed to Juventas Therapeutics, who subsequently sublicensed patent rights to SironRX for use in its field. The sublicensed patents contain intellectual property developed by both Cleveland Clinic and Juventas.\textsuperscript{91}

### 1.2.4 Initial Experiments with JVS-100

Under Juventas, initial published experimentation with SDF-1 and wound healing was performed with alginate scaffolds and applied to incisional wounds on Yorkshire pigs.\textsuperscript{92} A total of 12 full-thickness incisions were made on each animal, each incision 5cm in length.\textsuperscript{93} After incisions were closed, alginate patches incorporating SDF-1 plasmid, SDF-1 protein, or a saline control were administered along the wound.\textsuperscript{94} Wound length was measured before application of the alginate patches and when the animals were sacrificed.\textsuperscript{95} Figure 3 below presents data from this experiment and illustrates the significant decrease in wound length over a nine-day period when using either the plasmid or protein form of SDF-1, compared to saline.
Figure 3: Effect of SDF-1 protein and plasmid on wound healing as measured by wound length at 4 days and 9 days after incision.  

As seen in Figure 4 below, photographs of the wounds were taken before the alginate scaffolds were administered next to wounds and then nine days after, at which point the scaffolds were removed. A 2X magnification of the wounds at Day 9 shows improved healing, as measured by wound closure, when wounds were treated with SDF-1 protein or plasmid, compared to the wounds treated with a saline control (PBS).

Figure 4: Wounds treated with PBS, SDF-1 protein, and SDF-1 plasmid at day 0 and day 9 after incision.
To assess the level of fibrosis after wounding, immunohistochemical staining for vimentin was performed on experimental and control groups. Vimentin is an intermediate filament protein found in cells undergoing epithelial to mesenchymal transition (EMT), and evidence suggests it plays a role in fibrosis.\textsuperscript{99,100} Figure 5 below compares staining between wounds that received SDF-1 or control saline. Especially visible in the 2X magnification is reduced scarring among wounds that received SDF-1 in both the protein and plasmid formulation. During these preclinical studies, it was hypothesized that reduced scarring was the result of the upregulation of SDF-1 via Sonic hedgehog protein (Shh).\textsuperscript{101}

\textbf{Figure 5}: Immunohistochemical staining for vimentin in experimental and control groups.\textsuperscript{102} SDF-1 protein and plasmid groups show decreased vimentin staining (G and H), compared to the control (PBS) group (F).

After Juventas performed proof-of-concept studies with JVS-100 for dermatological applications, enough data was gathered from these experiments to spin-off SironRX. As Juventas was mainly focused on the cardiovascular applications of JVS-100 during these preclinical studies, SironRX was established to pursue dermatological applications of
JVS-100. SironRX performed additional preclinical trials using needles and needle-free injectors, with a non-viral naked DNA plasmid encoding for SDF-1. Data gathered from these preclinical studies resulted in the approval of the Company’s IND by the FDA in April of 2012 and the initiation of its clinical studies later that year.

The plasmid form of SDF-1 is used instead of the protein form for a few reasons. First, the patents surrounding the SDF-1 protein formulation are older than those for the plasmid form; therefore, the composition of matter protection of the recombinant protein technology will soon expire. Second, the protein formulation is not very stable and shelf life would be compromised. Lastly, the cost of manufacturing SDF-1 protein is much higher than it is for SDF-1 plasmid.

While using a plasmid to code for SDF-1 does have many advantages, there are some associated risks, as it is a form of gene therapy. One of these risks is insertional mutagenesis, an event that occurs through “ectopic chromosomal integration” of the therapeutic DNA. Insertional mutagenesis can interfere with the expression of certain genes, including tumor-suppressor genes and proto-oncogenes. However, this phenomenon occurs more often with viral gene therapy; by using a plasmid, or non-viral gene therapy, the risk of insertional mutagenesis is reduced. Moreover, the plasmid has shown to be safe in preclinical and clinical trials, both through Juventas and SironRX. The safety profile of the drug will continue to be monitored during the current Phase I clinical trial and beyond.
1.2.5 Drug Delivery

Drug delivery for the Phase I clinical trial occurs via a needle-free injector. Needle-free injectors decrease the variability between users as they standardized how the drug is delivered to patients, including angle of administration, depth of administration, and dosage.\textsuperscript{111} The device being utilized during the Phase I trial is the Bioject B2000 needle-free injector, an FDA approved device that utilizes disposable syringes and CO\textsubscript{2} cartridges.\textsuperscript{112} Each CO\textsubscript{2} cartridge allows for 5-7 injections; an alternative source of energy for large-scale use of the injector is a large CO\textsubscript{2} tank that is able to connect to the Bioject B2000 – this eliminates the need to frequently replace small CO\textsubscript{2} cartridges.\textsuperscript{113} JVS-100 is administered at a fixed dose of 0.5ml per injection and is delivered subcutaneously.\textsuperscript{114}

A handful of companies either sell or are developing needle-free injectors that could be appropriate for SironRX if it decides to partner with a needle-free injector manufacturer. In deciding the optimum device for its needs, SironRX must consider a number of factors including the following: the composition of the vial/container used to store the drug, the shelf life of the drug in such a vial, the number of injections per loaded device/vial, the power source used to deliver the drug (i.e. CO\textsubscript{2}, battery, etc.), the cost of the device and the drug vials and the number of times the device can be used before it needs to be charged.

When choosing how a drug is to be administered, the mode of delivery has to match the indication being targeted. For surgical incisions, an injection is appropriate, whereas
chronic wounds and burns may likely require topical formulations. While SironRX is currently focused on using an injectable to deliver JVS-100, topical applications can be investigated in the future for other indications in the wound healing market, such as chronic wounds like hard to heal ulcers or sores.

1.3 Benefits Per Costs

The use of JVS-100 for wound healing and scar prevention has numerous benefits:

1. The cost of each treatment may be priced similarly to other cosmetic focused injectable products (i.e. Botox, Juvederm) at approximately $1,500.115 Once the Company is closer to commercialization, it can study accurate prices with consultants to decide on a definite sales price for the injections. However, right now it is known that when the patient gets an injection of JVS-100, he or she is getting one round of treatment and the effects are permanent. In contrast, when a person gets injections of Botox or some other injectable drug used for cosmetic purposes, the effect is not lasting and the patient must get annual, or multiple, treatments.

2. SDF-1 mechanism of action allows for more rapid healing and reduced scarring.

3. The technology has the potential to be applied to both acute and chronic wounds.

4. JVS-100 works as a prophylactic measure, rather than a treatment. Therefore, patients save the costs of ineffective therapies for treating scars.

5. The mode of administration with a needle-free injector is quick and easy to use.

6. Only one round of injections is required for improved wound healing and scar reduction.

7. The use of a plasmid facilitates large-scale manufacturing.
8. The technology triggers autologous stem cells versus allogenically provided stem cells; therefore, rejection is not an issue.

9. To date, preclinical and clinical trials have demonstrated the use of JVS-100 is safe.\textsuperscript{116}

1.4 Competition

The competitive landscape in the wound healing and scar prevention market will determine how JVS-100 will perform upon commercialization, as well as help to assess how SironRX can create an advantage over competing technologies. Table 2 below provides an overview of some of the companies and institutions pursuing wound healing and scar treatment with technologies based on biological mechanisms. Among those listed are five companies that are strong competitive forces that may prove to be contenders in the wound healing and scar prevention market.
### Table 2: Companies with technologies focused on wound healing and scar treatment

<table>
<thead>
<tr>
<th>Company</th>
<th>Technology</th>
<th>Areas of Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excaliard/Pfizer¹¹³</td>
<td>anti-sense to CTGF</td>
<td>Scar prevention</td>
</tr>
<tr>
<td>RXi Pharmaceuticals¹¹⁸</td>
<td>RNAi to CTGF</td>
<td>Scar prevention</td>
</tr>
<tr>
<td>Wound Management Technologies¹¹⁹</td>
<td>Active collagen fragments (Cellerate RX)</td>
<td>Surgical wound healing</td>
</tr>
<tr>
<td>Sirnaomics¹²⁰</td>
<td>Nano-particle based siRNA (STP-705)</td>
<td>Wound healing and scar reduction</td>
</tr>
<tr>
<td>RegeneRx¹²¹</td>
<td>Peptide Thymosin Beta 4</td>
<td>Wound healing</td>
</tr>
<tr>
<td>Kuros¹²²</td>
<td>Fibrin matrix/PDGF</td>
<td>Wound healing</td>
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<tr>
<td>Garnet BioTherapeutics, Inc.¹²³</td>
<td>Cell Therapy (GBT 009)</td>
<td>Scar prevention</td>
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<tr>
<td>AdeTherapeutics (University of Saskatchewan)¹²⁴</td>
<td>Amino Acid (CXC chemokine receptor antagonists)</td>
<td>Scar reduction</td>
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<td>Avita Medical¹²⁵</td>
<td>ReCell - cell therapy</td>
<td>Wound healing and scar reduction</td>
</tr>
<tr>
<td>Suneva Medical¹²⁶</td>
<td>ReGenica - protein therapy</td>
<td>Wound healing</td>
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<td>Ludwig Maximilian Univ of Munich¹²⁷</td>
<td>&quot;S100&quot; Protein therapy</td>
<td>Scar prevention</td>
</tr>
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<td>Systagenix/MiMedx¹²⁸</td>
<td>EpiFix - human amniotic membrane allograft</td>
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<td>DSC127 - Peptide (Angiotensin analog) therapy</td>
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<td>HealOr Ltd¹³⁰</td>
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<td>Surgical wound healing</td>
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<td>FirstString Research¹³¹</td>
<td>Granexin Gel - Peptide ACT1</td>
<td>Wound healing and scar reduction</td>
</tr>
<tr>
<td>The Victoria University of Manchester¹³²</td>
<td>Growth factor neutralizing antibody</td>
<td>Scar reduction</td>
</tr>
<tr>
<td>CoDa Therapeutics¹³³</td>
<td>Unmodified oligonucleotide (Nexagon)</td>
<td>Wound healing, scar reduction</td>
</tr>
<tr>
<td>University of Bristol¹³⁴</td>
<td>DNA antisense to osteopontin</td>
<td>Scar reduction</td>
</tr>
<tr>
<td>Keracure¹³⁵</td>
<td>Living human keratinocytes</td>
<td>Wound healing</td>
</tr>
<tr>
<td>GliaMed¹³⁶</td>
<td>Regenerative Immunophilin Ligands</td>
<td>Wound healing, scar reduction</td>
</tr>
<tr>
<td>ScarX Therapeutics¹³⁷</td>
<td>Nefopam – inhibits beta catenin</td>
<td>Scar prevention</td>
</tr>
</tbody>
</table>

The competition can be viewed in two ways: companies whose technologies address only scar prevention, and companies whose technologies address both scar treatment and wound healing. Because JVS-100 has shown efficacy in preclinical models of both scar prevention and wound healing, it is necessary to assess competitive forces that address both therapeutic endpoints.
1.4.1 Scar Treatment

Pfizer, Inc. – In November 2011, Pfizer completed its acquisition of Excaliardi Pharmaceuticals from Isis Pharmaceuticals in a deal for $316M for its lead compound, ECX-001.\textsuperscript{138,139} EXC-001 is an antisense compound that targets a specific protein, connective tissue growth factor (CTGF), and works to prevent the translation of mRNA into proteins.\textsuperscript{140} CTGF is involved in cell proliferation, differentiation, and angiogenesis and is induced during tissue regeneration.\textsuperscript{141} The normal wound healing process requires certain levels of CTGF.\textsuperscript{142} It is the overabundance of this growth factor that contributes to fibrosis, as CTGF is responsible for transforming normal epithelial cells into cells that produce scar tissue.\textsuperscript{143} Both hypertrophic scars and keloids contain high levels of CTGF.\textsuperscript{144} Excaliardi completed three Phase II clinical trials with EXC-001.\textsuperscript{145}

Antisense technology utilizes a single-stranded oligonucleotide, either DNA or RNA.\textsuperscript{146} The oligonucleotide is hybridized with mRNA and interferes with normal gene function by disrupting the mRNA/ribosome association, or by degrading the mRNA through cleavage or enzymes.\textsuperscript{147} Both mechanisms affect normal RNA function and prevent the translation of mRNA into proteins.\textsuperscript{148} However, traditional single-stranded antisense compounds have poor potency.\textsuperscript{149} Phase III clinical trials will help to illuminate more of the safety and efficacy surrounding EXC-001.

RXi Pharmaceuticals – RXi Pharmaceuticals is a biotechnology company developing therapies using RNA targeting technology. Its lead product, RXI-109, is a RNA interference (RNAi) antisense hybrid that also targets CTGF.\textsuperscript{150} In June of 2012, the
company began a Phase I clinical trial of RXI-109, which is being investigated for its ability to minimize dermal scarring following abdominoplasties. RNAi is a naturally occurring process that occurs when double-stranded RNA prevents mRNA from being translated, thus protein synthesis does not occur. Unlike EXC-001, RXi-109 contains both double-stranded and single-stranded regions, allowing for improved distribution and cellular uptake of the compound. However, one limitation of RXi’s technology is that multiple doses over time are required. In contrast, SironRX is able to offer a technology that requires only a one-time dose to help heal wounds and prevent scar formation.

*ScarX Therapeutics* – ScarX Therapeutics is a preclinical stage company repurposing an analgesic called Nefopam for the prevention of dermal scarring after surgery. Its lead product, MI-001, works by inhibiting the synthesis of beta catenin, a protein whose levels are spiked in hypertrophic scars after wounding. In vitro and in vivo studies of MI-001 involve topical administration of the drug in the form of a cream. Later stage clinical trials in humans will be needed to assess the true efficacy of MI-001 as a prophylactic scar treatment.

**1.4.2 Wound Healing and Scar Reduction**

*Sirnaomics* – Sirnaomics is a biopharmaceutical company focused on developing therapeutics using RNAi technology. It is reported the company may begin a Phase I clinical trial in 2013 for its scarless wound-healing drug, STP-705. STP-705 is a small interfering RNA (siRNA) molecule comprised of a double stranded oligonucleotide that
targets both TGF-β1 and Cox-2 (cyclooxygenase). Cox-2 is an enzyme responsible for producing prostaglandin PGE2. Cox-2 is up-regulated in response to inflammation and both Cox-2 and PGE2 have been shown to be involved in scar formation. TGF-β1 is a cytokine responsible for cell proliferation and differentiation. Additionally, this protein is involved in the synthesis of collagen and its overproduction has been shown to result in excessive scar tissue and fibrosis. RNAi technology is limited by bulky double-stranded oligonucleotides, which presents complications for effective tissue distribution and cellular uptake.

**CoDa Therapeutics** – CoDa Therapeutics is a biopharmaceutical company focused on developing therapies for wound care and tissue repair using gap junction modulation. Its lead product, Nexagon, is an oligonucleotide that down-regulates the gap junction protein Connexin (Cx) 43 via antisense technology. Cx43 is normally downregulated at the edges of acute wounds. With Nexagon, Cx43 is downregulated faster and there is an increase in fibroblast and keratinocyte proliferation and migration at the wound site. Like Pfizer and its drug EXC-001, CoDa Therapeutics will have to overcome the known limitations of antisense technology.

The value proposition SironRX offers – based on the unmet need of wound healing and scar prevention, how the Company approaches this need, the benefits per costs of its technology, and how these benefits are superior to the competition – gives insight on the commercialization potential of JVS-100 in the wound healing and scar therapy markets. Successful commercialization of JVS-100 will depend on, among other things, the value
it brings to customers in this market space. These customers will find that adopting SironRX’s technology will add value to their lives.

2. Customers

SironRX’s primary customers are physicians using its technology. Doctors have a need to provide improved care to their patients and as customers, must be convinced of the added value a new medical technology will bring. Surgeons performing the procedures ultimately decide whether or not they will provide the option of using JVS-100 to their patients.

Hospital administrators and patients are also factored into the customer equation. Hospital administrators have decision-making power when it comes to what products will enter the hospital, largely focused from a price and cost savings perspective. As end-users, patients are also part of the purchasing decision.

2.1 Reimbursement

Reimbursement from health insurance carriers is determined by the medical necessity of a product or procedure and whether it is considered experimental or proven effective through clinical trials and peer-reviewed literature.\textsuperscript{169,170} In the case of scarring, treatment is considered medically necessary only if the scar impedes normal functioning of the body.\textsuperscript{171} Otherwise, scar revision procedures and treatments are considered cosmetic and do not qualify for reimbursement. While physicians and hospital administrators do consider reimbursement when deciding which products to purchase,
cosmetic procedures and products are not as relevant because patients are willing to pay out-of-pocket for such services. In a recent survey of physicians who performed cosmetic procedures, it was concluded that 75% of patients self-pay for such services.\textsuperscript{172}

\subsection*{2.2 Aesthetic Surgery Market}

Regarding aesthetic and plastic surgery, the U.S. and Brazil potentially serve as the largest markets for JVS-100. Medical tourism is popular in Brazil, as patients can receive care comparable to that in the U.S.\textsuperscript{173} Figure 6 below details the type and number of plastic surgery procedures performed in 2010 in the U.S. and Brazil. The need for JVS-100 is underscored in the plastic surgery market, as procedures in this industry are usually performed because the patient wants to improve the physical appearance of his or her body. Avoiding the appearance of a scar would align with the objective of aesthetic procedures. The plastic surgery market is an ever-growing space, where there was a 3% increase in the number of procedures just from 2011 to 2012.\textsuperscript{174}
### Estimated Number of Plastic Surgeons

<table>
<thead>
<tr>
<th>Numerical Value</th>
<th>U.S.*</th>
<th>Brazil</th>
<th>...</th>
</tr>
</thead>
<tbody>
<tr>
<td>33,027</td>
<td>5970</td>
<td>5024</td>
<td></td>
</tr>
</tbody>
</table>

#### Surgical Procedures

<table>
<thead>
<tr>
<th>Description</th>
<th>Total</th>
<th>U.S.*</th>
<th>Brazil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominoplasty</td>
<td>681,344</td>
<td>154,265</td>
<td>125,600</td>
</tr>
<tr>
<td>Blepharoplasty</td>
<td>1,085,153</td>
<td>127,937</td>
<td>155,543</td>
</tr>
<tr>
<td>Breast augmentation</td>
<td>1,506,475</td>
<td>336,648</td>
<td>254,214</td>
</tr>
<tr>
<td>Breast lift</td>
<td>543,848</td>
<td>128,295</td>
<td>91,939</td>
</tr>
<tr>
<td>Breast reduction (women)</td>
<td>549,994</td>
<td>107,699</td>
<td>83,650</td>
</tr>
<tr>
<td>Buttock augmentation</td>
<td>119,007</td>
<td>19,104</td>
<td>44,663</td>
</tr>
<tr>
<td>Buttock lift</td>
<td>36,977</td>
<td>7,701</td>
<td>6,581</td>
</tr>
<tr>
<td>Cheek implants</td>
<td>40,891</td>
<td>4,119</td>
<td>8,089</td>
</tr>
<tr>
<td>Chin augmentation</td>
<td>108,178</td>
<td>20,298</td>
<td>19,393</td>
</tr>
<tr>
<td>Facelift</td>
<td>421,029</td>
<td>79,759</td>
<td>71,793</td>
</tr>
<tr>
<td>Forehead lift</td>
<td>135,242</td>
<td>30,089</td>
<td>25,120</td>
</tr>
<tr>
<td>Gynecomastia, treatment of (male breast</td>
<td>235,947</td>
<td>28,596</td>
<td>31,601</td>
</tr>
<tr>
<td>Hair transplantation</td>
<td>77,480</td>
<td>2,448</td>
<td>5,778</td>
</tr>
<tr>
<td>Lip augmentation</td>
<td>221,703</td>
<td>27,522</td>
<td>36,223</td>
</tr>
<tr>
<td>Lipoplasty</td>
<td>2,174,803</td>
<td>402,259</td>
<td>436,887</td>
</tr>
<tr>
<td>Lower body lift</td>
<td>64,475</td>
<td>11,045</td>
<td>9,696</td>
</tr>
<tr>
<td>Otoplasty</td>
<td>242,271</td>
<td>22,029</td>
<td>40,745</td>
</tr>
<tr>
<td>Rhinoplasty</td>
<td>985,325</td>
<td>75,521</td>
<td>106,609</td>
</tr>
<tr>
<td>Thigh lift</td>
<td>70,558</td>
<td>10,686</td>
<td>10,098</td>
</tr>
<tr>
<td>Upper arm lift</td>
<td>94,026</td>
<td>19,641</td>
<td>13,012</td>
</tr>
<tr>
<td>Vaginal rejuvenation</td>
<td>67,665</td>
<td>5,194</td>
<td>14,871</td>
</tr>
<tr>
<td><strong>Total Surgical Procedures</strong></td>
<td>9,462,391</td>
<td>1,620,855</td>
<td>1,592,106</td>
</tr>
</tbody>
</table>

**Figure 6:** Number of plastic surgery procedures performed in 2010 in the U.S. and Brazil. The totals listed include surgeries performed in other countries that are not included in this figure.

### 3. Current Structure and Organization of SironRX

SironRX is currently headquartered out of the Global Cardiovascular Innovation Center (GCIC) in Cleveland, OH, “a cardiovascular product development consortium.”

While SironRX utilizes office and laboratory space at the center for its day-to-day activities, the Company communicates with medical facilities off-site for its clinical trial work.

#### 3.1 Key Partnerships in the Phase I Clinical trial

The outcome of the Phase I study will depend on key partnerships. Currently there are six study sites up and running for the Phase I trial. This study requires participation of hospitals, physicians, and clinical trials specialists. SironRX works with clinical trials...
specialists at the study sites to coordinate consent and enrollment, while helping with overall maintenance of the study data collection.

3.2 SironRX Current Phase I Clinical Trial

The title of SironRX’s Phase I clinical trials is “Phase I randomized, double-blind, placebo controlled, dose escalation study with adults receiving surgical sternotomy incisions.”\(^{178}\) The trial will assess both the safety and efficacy among individuals receiving incisions for cardiovascular surgery.

While the design of the study ensures determination of the efficacy of JVS-100, the patient population adds complexity to the current trial. Since serious heart problems are an indication for cardiovascular surgery, patients may be less interested in enrolling in a clinical trial than they are about improving the condition of their heart. That being said, SironRX has been able to enroll 70% of the patients in the trial to date. Going forward, Phase II trials may be designed so that patients undergoing less life-threatening surgeries are included, helping to secure quicker enrollment of subjects to participate in the trials.

Future clinical trial design and a clear product development strategy are necessary for SironRX to secure additional funding from investors.\(^{179}\) SironRX has the advantage of having its product already tested in a Phase I clinical trial through Juventas Therapeutics, which demonstrated safety among its subjects.\(^{180}\) JVS-100 is currently being investigated in two Phase II trials by Juventas, creating even more of an advantage for SironRX, as the Phase II trials will provide insight on the drug’s effectiveness among patients.\(^{181}\) Having
most of the R&D for JVS-100 completed before its inception, SironRX has been able to quickly complete preclinical testing on animals and develop and implement a Phase I clinical trial, as there is substantial evidence from Juventas that JVS-100 is effective at tissue repair.\textsuperscript{182}

### 3.3 Current Financing for SironRX

SironRX closed a $3.4M Series A round of financing in August 2011.\textsuperscript{183} Contributing investors included Northcoast Angels, Early Stage Partners, Fletcher Spaght Ventures, Glengary and Ohio Tech Angels.\textsuperscript{184} SironRX also received a $1 million grant from the State of Ohio the same year.\textsuperscript{185} This financing will allow SironRX to complete its Phase I clinical trial, which has a completion date targeted for the end of Q3 2013.\textsuperscript{186}

### 3.4 Current Financials

Figure 7 below is a presentation of what the operating expenses and revenue for a company at the stage of SironRX might look like. The three largest expense items are clinical trials, employees and intellectual property, which includes legal counsel and license and patent fees. These three categories usually exhibit the highest expenses for biotech startups since they require clinical trials for continued product development, protection of the products being investigated, and personnel to carry out the functions for successful advancement of the technology. Because SironRX is an early stage biotechnology company working to develop a new drug, these items should require the most cash.
<table>
<thead>
<tr>
<th><strong>Revenue</strong></th>
<th><strong>ACTUAL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant Revenue</td>
<td>$500,000</td>
</tr>
<tr>
<td>Subcontracting Revenue</td>
<td>$500,000</td>
</tr>
<tr>
<td><strong>Total Revenue</strong></td>
<td>$1,000,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Operating Expenses</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Employee Payroll &amp; Benefits</strong></td>
<td>$594,550 (23%)</td>
</tr>
<tr>
<td>Consulting</td>
<td>$258,500 (10%)</td>
</tr>
<tr>
<td>Research &amp; Development</td>
<td>$258,500 (10%)</td>
</tr>
<tr>
<td><strong>Clinical Trial Costs</strong></td>
<td>$801,350 (31%)</td>
</tr>
<tr>
<td>Office Expenses</td>
<td>$38,775 (1.5%) (Rent, Supplies, FedEx/Postage, IT)</td>
</tr>
<tr>
<td>Travel</td>
<td>$129,250 (5%)</td>
</tr>
<tr>
<td><strong>Professional Fees</strong></td>
<td>$206,800 (8%) (Corp. Legal, Audit/Tax, Insurance)</td>
</tr>
<tr>
<td>License &amp; Patent Fees</td>
<td>$232,650 (9%)</td>
</tr>
<tr>
<td>Marketing &amp; Promotion</td>
<td>$12,925 (0.5%)</td>
</tr>
<tr>
<td>Other Operating Expenses</td>
<td>$25,850 (1%) (Subscriptions, Conferences, Misc.)</td>
</tr>
<tr>
<td><strong>Depreciation &amp; Amortization</strong></td>
<td>$25,850 (1%)</td>
</tr>
<tr>
<td><strong>Total Operating Expenses</strong></td>
<td>$2,585,000</td>
</tr>
<tr>
<td><strong>Net Operating Income/ (Loss)</strong></td>
<td>($1,585,000)</td>
</tr>
<tr>
<td>Other Income / (Expense)</td>
<td></td>
</tr>
<tr>
<td><strong>Net Income/ (Loss)</strong></td>
<td>($1,585,000)</td>
</tr>
</tbody>
</table>

**Figure 7**: Hypothetical P&L statement for SironRX

Based on the hypothetical P&L statement, SironRX would currently operate at a loss, which would be typical of an early stage biotech company. Since biotech startups usually do not have products available on the market, revenue streams are found mainly through grants, small partnerships and consulting work.187
4. Analysis of SironRX’s Strategy

Identifying a company’s strategy, or how it performs different activities from competitors or similar activities in different ways, is important as it helps to understand a company’s competitive advantage. ¹⁸⁸

4.1 SWOT Analysis

A SWOT analysis helps to build a company’s strategy by determining how it can maximize its strengths and opportunities while minimizing threats and weaknesses. It is both an internal and external analysis of a company’s strategy.

4.1.1 Strengths

1. JVS-100 is a prophylactic treatment
2. JVS-100 has the potential to be delivered via multiple modes of application
3. Relatively low overall cost to patients due to one-time use of JVS-100
4. Patent protection of JVS-100 product

4.1.2 Weaknesses

1. Reimbursement may be low due to the cosmetic application of JVS-100
2. Current design of Phase I clinical trial adds challenges to enrolling patients
3. Limited resources require significant focus on part of the total market opportunity
4.1.3 Opportunities

1. Currently, there is no prophylactic scar therapy on the market
2. The number of surgical procedures in the U.S. continues to grow
3. A secondary market is available and expansion is possible (i.e. chronic wounds)

4.1.4 Threats

1. Emerging products, like EXC-001, may take away from market share
2. Established rivals have experience in the wound healing market
3. Available substitutes on the market for scar treatment

Figure 8 below is a SWOT matrix, listing the strengths, weaknesses, opportunities, and threats of SironRX. Through this matrix, one can generate strategies that use a company’s strengths to take advantage of opportunities while minimizing threats. Just as important are the strategies a company can formulate that consider its weaknesses and use them to create opportunities and avoid threats. By considering the strategies outlined below, SironRX may be able to create more value for its customers and take advantage of the wound healing and scar therapy markets.
4.1.5 SWOT Matrix and Strategies

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Scar prevention</td>
<td>1. Phase I clinical trial design</td>
</tr>
<tr>
<td>2. Multiple modes of application</td>
<td>2. Reimbursement (cosmetic)</td>
</tr>
<tr>
<td>3. Low overall cost</td>
<td>3. Limited resources</td>
</tr>
<tr>
<td>4. Patent protection of JVS-100 product</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>SO Strategies</th>
<th>WO Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No current prophylactic scar therapy</td>
<td>1. Address unmet need to take advantage of an underserved market</td>
<td>1. Design Phase II and III clinical trials with broader enrollment guidelines</td>
</tr>
<tr>
<td>2. Secondary market/expansion possible (i.e. chronic wounds)</td>
<td>2. Extend technology to multiple platforms</td>
<td>2. R&amp;D to address indications considered medically necessary (i.e. chronic wounds)</td>
</tr>
<tr>
<td>3. Increase in the number of surgical procedures</td>
<td>3. Market product as an affordable, one-time treatment</td>
<td>3. Focus on product development to take advantage of increased market size at product launch</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Threats</th>
<th>ST Strategies</th>
<th>WT Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Substitutes available in the market</td>
<td>1. Decrease buyer’s need of substitutes by preventing the formation of scars</td>
<td>1. Organize later stage clinical trials to fully demonstrate benefits over substitutes.</td>
</tr>
<tr>
<td>2. Emerging products</td>
<td>2. Offer more than one method of delivering therapy</td>
<td>2. Offer competitive prices compared to emerging products</td>
</tr>
<tr>
<td>3. Established rivals</td>
<td>3. Disrupt market with transformative value of technology offering</td>
<td>3. Form strategic partnerships with large firms to complete late stage clinical trials</td>
</tr>
</tbody>
</table>

**Figure 8**: SWOT diagram

4.2 VRIO

VRIO (value, rarity, inimitability, organization) is an analytical tool to help assess the competitive and economic implications of a company’s resources or capabilities, the drivers of value creation for a company. In this context, resources are assets that are not easily duplicated or acquired. Capabilities are activities that a company does better than...
other firms. In the case of SironRX, two of its resources are the patents protecting its technology and the Company’s human capital, which includes the doctors, scientists, and management team. Its capabilities include being able to accelerate wound healing \textit{and} reduce scar formation with a single product and drive product development with limited resources.

**Table 3:** VRIO framework for SironRX’s resources and capabilities.

<table>
<thead>
<tr>
<th>Resource</th>
<th>Valuable?</th>
<th>Rare?</th>
<th>Costly to Imitate?</th>
<th>Exploited by Organization?</th>
<th>Competitive Implications</th>
<th>Economic Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patents</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Sustained Advantage</td>
<td>Above Normal</td>
</tr>
<tr>
<td>Human Capital</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td>Parity</td>
<td>Normal</td>
</tr>
<tr>
<td>Exploit SDF-1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Sustained Advantage</td>
<td>Above Normal</td>
</tr>
<tr>
<td>Product Development</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>Temporary Advantage</td>
<td>Above Normal</td>
</tr>
</tbody>
</table>

Based on this analysis, SironRX’s ability to harness the power of SDF-1 to meet an unmet need and the patents protecting this technology are the resources that contribute most to the Company’s competitive advantage and have the greatest economic implications.

4.3 Strategic Fit

Another test of a company’s strategy is determining fit. An activity map illustrates a company’s fit, that is, the connection between its activities that lowers the odds a strategy
will be copied. The more connected the activities, the stronger the fit. Below in Figure 9 is a representation of the strategic fit of SironRX’s activities based on certain facets of its value proposition, which include customers (physicians and surgeons), their needs (a wound healing and scar prevention drug), and the relative price of such a product (low relative to alternatives). Based on the connectedness of the activities associated with these factors, SironRX demonstrates a strong strategic fit.

![Activity map demonstrating fit among SironRX’s activities](image)

**Figure 9:** Activity map demonstrating fit among SironRX’s activities

5. Next Steps

After completion of its Phase I clinical trials, SironRX should focus on product development through the design of its Phase II and Phase III studies, as these later stage
clinical trials will ultimately reveal whether JVS-100 is safe and effective among a diverse population of subjects.

5.1 Phase II and Phase III Clinical Trials

Phase II clinical trials further illuminate the safety profile of a new drug and aim to determine the effectiveness of the drug within a diseased population. In order for SironRX to gain a comprehensive understanding of how JVS-100 heals wounds and prevents scar formation, multiple trials should be run together among various patient populations. While Phase I clinical trials focus solely on sternotomy incisions, Phase II trials should be designed to include various types of surgical procedures that result in incisions on different areas of the body. These could include cosmetic or reconstructive surgeries. Using different incision sites will allow for a better assessment of the drug’s capabilities among different wound sites. During this phase, SironRX will continue to establish the optimal dose for JVS-100. Phase II clinical trials typically involve between 100 to 500 patients and usually require two years to complete.

Phase III clinical trials are comprehensive studies involving between 1,000 to 3,000 patients. The design of Phase III trials will be determined by the outcome of previous Phase II studies. Effectiveness of JVS-100 will be confirmed during this stage of clinical investigation. The diverse population of subjects helps to understand how the drug will behave in a real world setting. Upon validation of the drug’s effectiveness and safety profile, SironRX will submit a Biologics License Application (BLA) to the FDA for review. It is after this review process that a new drug can be manufactured on a large
scale and marketed and sold to customers. Below in Table 4 is a summary of the timeline of a typical drug from screening for potential compounds to market launch.

**Table 4: Drug Development Process (adapted from From Alchemy to IPO)**

<table>
<thead>
<tr>
<th>Clinical trials</th>
<th>Early research/pre-clinical testing</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>FDA review process and approval</th>
<th>On market</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>6.5</td>
<td>1.5</td>
<td>2</td>
<td>3.5</td>
<td>1.5</td>
<td>Took 15 years to get here</td>
<td></td>
</tr>
<tr>
<td>Test population</td>
<td>Test tube and animal studies</td>
<td>20 to 80 healthy volunteers</td>
<td>100 to 300 patients</td>
<td>1,000 to 3,000 patients</td>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpose</td>
<td>Look for safety, desired activity</td>
<td>Determine safety and dosage for the next phase</td>
<td>Evaluate effectiveness, look for potential toxic side effects</td>
<td>Confirm effectiveness, look for side effects from long-term use</td>
<td>Post-marketing surveillance of the patients to look for potential problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success rate</td>
<td>5,000 evaluated</td>
<td>5 compounds enter clinical trials</td>
<td></td>
<td>1 compound approved</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.2 Financing Phase II and Phase III Clinical Trials

In order to carry out late stage clinical trials, SironRX will need to secure additional financing. Costs of Phase II studies vary among different therapeutic areas, but average costs are about $36,000 per patient. With 100-300 patients needed to conduct a Phase II study, the cost of evaluating a drug at this level can range from $3.6 to $10.8 million.
After successful completion of Phase II studies, SironRX will decide the next step regarding Phase III clinical trials. Phase III studies require substantial cash to complete – the average cost per patient across therapeutic areas is about $47,000. With 1,000 to 3,000 patients required for this stage of investigation, one Phase III study could cost, on average, anywhere from $47 to $141 million. Because completion of Phase III studies is cost prohibitive for biotech startups, certain options are made available that allow investigational drugs to enter these late stage trials.

Further illustrating the cost of drug development are the estimates made in a survey of 10 pharmaceutical firms and their respective 68 new drugs. In this study, it was found that the out-of-pocket cost of clinical trials per approved new drug is $282 million. When out-of-pocket preclinical costs were factored in, creating a full cost estimate, the out-of-pocket cost per approved new drug increased to $403 million. Clearly, these numbers demonstrate that in order for SironRX to continue development of JVS-100, it must choose sources of financing that generate the greatest amount of cash. The Company has several options to fund its next stages of development, including venture capital, issuing an IPO, or entering into a partnership with a corporation.

5.2.1 Venture Capital

If the Phase I trial proves successful and meets its endpoints, SironRX may be able to secure additional financing through venture capital to fund Phase II studies. Using Juventas as an example, after successful completion of Phase I studies demonstrating the safety and efficacy of JVS-100 for heart failure, Juventas obtained $22 million from
venture firms in a Series B round lead by Triathlon Medical Venture Partners and New Science Ventures to carry out Phase II studies.²⁰¹

5.2.2 Corporate VC

Many large healthcare and pharmaceutical companies have corporate venture arms that invest in promising technologies. Most of these large firms invest at an early stage. Table 5 below is a list of corporations with funds solely for investing in new companies with expertise in biotech, medical device, and/or healthcare. Like traditional venture capital firms, venture arms of large corporations strive to create financial partnerships with a company.
<table>
<thead>
<tr>
<th>Pharmaceutical Company</th>
<th>Venture Arm</th>
<th>Total Money Under MGMT (millions)</th>
<th>Date of Last Fund</th>
<th>Size of Fund (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>Amgen Ventures</td>
<td>$200</td>
<td>2012</td>
<td>$100</td>
</tr>
<tr>
<td>Astellas Pharma</td>
<td>Astellas Venture Mgmt</td>
<td>Four funds total $100</td>
<td>2005</td>
<td>N/A</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>MedImmune Ventures</td>
<td>$400</td>
<td>2002</td>
<td>$400</td>
</tr>
<tr>
<td>Baxter International</td>
<td>Baxter Ventures</td>
<td>$200</td>
<td>2011</td>
<td>N/A</td>
</tr>
<tr>
<td>Boehringer-Ingelheim</td>
<td>Boehringer Ingelheim Venture Fund</td>
<td>100 euro</td>
<td>Established 2010</td>
<td>N/A</td>
</tr>
<tr>
<td>Eli Lilly and Company</td>
<td>Lilly Ventures</td>
<td>$200</td>
<td>Established 2001</td>
<td>N/A</td>
</tr>
<tr>
<td>Genzyme</td>
<td>Sanofi-Genzyme BioVentures</td>
<td>$100</td>
<td>2001</td>
<td>$100</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
<td>SR One</td>
<td>$680</td>
<td>N/A</td>
<td>$30-$50/year</td>
</tr>
<tr>
<td>Merck KGaA</td>
<td>MS Ventures</td>
<td>100 euro</td>
<td>May 2013</td>
<td>60 euro</td>
</tr>
<tr>
<td>Merck &amp; Co.</td>
<td>Merck Research Ventures Fund</td>
<td>$250</td>
<td>Established 2011</td>
<td>N/A</td>
</tr>
<tr>
<td>Mitsubishi Pharma</td>
<td>MP Healthcare Venture Mgmt.</td>
<td>$100</td>
<td>2006</td>
<td>$5 per company</td>
</tr>
<tr>
<td>Novartis</td>
<td>Novartis Venture Fund</td>
<td>$600</td>
<td>Established 1996</td>
<td>N/A</td>
</tr>
<tr>
<td>Novartis</td>
<td>Novartis Option Fund</td>
<td>$200</td>
<td>Established 2007</td>
<td>N/A</td>
</tr>
<tr>
<td>Novo</td>
<td>Novo Ventures</td>
<td>$800</td>
<td>N/A</td>
<td>Up to $140 annually</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Pfizer Venture Investments</td>
<td>N/A</td>
<td>Started in 2004</td>
<td>$50 annual budget</td>
</tr>
<tr>
<td>Roche</td>
<td>Roche Venture Fund</td>
<td>500 CHF (~$530)</td>
<td>Established 2002</td>
<td>N/A</td>
</tr>
<tr>
<td>Shire</td>
<td>Strategic Investment Group</td>
<td>$50</td>
<td>Established 2011</td>
<td>N/A</td>
</tr>
<tr>
<td>Takeda</td>
<td>Takeda Ventures</td>
<td>$54</td>
<td>Established 2001</td>
<td>N/A</td>
</tr>
</tbody>
</table>

5.2.3 Initial Public Offering (IPO)

Another option for SironRX is to issue an initial public offering (IPO) with the help of investment bankers. In this case, a company decides to sell shares of its stock to the public. This route of financing has its advantages and disadvantages, as an IPO depends on the current state of the market and the perceived value of the industry sector. If a biotech company shows promise of successfully completing late stage clinical trials, it
can issue an IPO at a relatively high price and raise the money needed to fund product development. However, because the company becomes publicly traded, it must disclose pertinent information regarding its clinical trials, as stipulated by the SEC. If the clinical trials do not meet certain endpoints or there are complications during the studies, the company’s stock price could quickly drop. 2013 has seen an increase in the number of biotech IPOs being issued after many years of low activity in the industry. Figure 10 below lists biotechnology companies that have recently issued IPOs and their stock market price that closed on July 19, 2013.

<table>
<thead>
<tr>
<th>Company</th>
<th>Ticker</th>
<th>Location</th>
<th>IPO Price</th>
<th>Friday’s close</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epizyme</td>
<td>EPZM</td>
<td>Cambridge, MA</td>
<td>$15</td>
<td>$38.75</td>
</tr>
<tr>
<td>Kamada</td>
<td>KMDA</td>
<td>Ness Ziona, Israel</td>
<td>$9.25</td>
<td>$13.05</td>
</tr>
<tr>
<td>Alcobra</td>
<td>ADHD</td>
<td>New York</td>
<td>$8</td>
<td>$9.97</td>
</tr>
<tr>
<td>Portola Pharmaceuticals</td>
<td>PTLA</td>
<td>South SF</td>
<td>$14.50</td>
<td>$22.95</td>
</tr>
<tr>
<td>Ambit Biosciences</td>
<td>AMBI</td>
<td>San Diego</td>
<td>$8</td>
<td>$12</td>
</tr>
<tr>
<td>Receptos</td>
<td>RCPT</td>
<td>San Diego</td>
<td>$14</td>
<td>$19.60</td>
</tr>
<tr>
<td>Insys Therapeutics</td>
<td>INSY</td>
<td>Phoenix, AZ</td>
<td>$8</td>
<td>$17.14</td>
</tr>
<tr>
<td>Omthera Pharmaceuticals</td>
<td>OMTH</td>
<td>Princeton, NJ</td>
<td>$8</td>
<td>acquired at $12.70</td>
</tr>
<tr>
<td>Chimera</td>
<td>CMRX</td>
<td>Durham, NC</td>
<td>$14</td>
<td>$24.55</td>
</tr>
<tr>
<td>KaluBios Pharmaceuticals</td>
<td>KBIO</td>
<td>South SF</td>
<td>$8</td>
<td>$5.83</td>
</tr>
<tr>
<td>Quintiles</td>
<td>Q</td>
<td>Durham, NC</td>
<td>$40</td>
<td>$44.07</td>
</tr>
<tr>
<td>Enanta Pharmaceuticals</td>
<td>ENTA</td>
<td>Watertown, MA</td>
<td>$14</td>
<td>$17.65</td>
</tr>
<tr>
<td>Tetraphase Pharmaceuticals</td>
<td>TPH</td>
<td>Watertown, MA</td>
<td>$7</td>
<td>$7.79</td>
</tr>
<tr>
<td>Stermeo Therapeutics</td>
<td>STML</td>
<td>New York</td>
<td>$10</td>
<td>$28.03</td>
</tr>
<tr>
<td>GW Pharmaceuticals</td>
<td>GPH</td>
<td>London</td>
<td>$8.90</td>
<td>$8.85</td>
</tr>
<tr>
<td>Cancer Genetics</td>
<td>CGX</td>
<td>Rutherford, NJ</td>
<td>$10</td>
<td>$10.87</td>
</tr>
<tr>
<td>Liposcience</td>
<td>LPDX</td>
<td>Raleigh, NC</td>
<td>$9</td>
<td>$6.12</td>
</tr>
<tr>
<td>Bluebird Bio</td>
<td>BLUE</td>
<td>Cambridge, MA</td>
<td>$17</td>
<td>$33.99</td>
</tr>
<tr>
<td>PTC Therapeutics</td>
<td>PTCT</td>
<td>Princeton, NJ</td>
<td>$15</td>
<td>$17.75</td>
</tr>
<tr>
<td>NanoString Technologies</td>
<td>NTSG</td>
<td>Seattle</td>
<td>$10</td>
<td>$9.44</td>
</tr>
<tr>
<td>Prosensa</td>
<td>RNA</td>
<td>Leiden, The Netherlands</td>
<td>$13</td>
<td>$25.85</td>
</tr>
<tr>
<td>Aratana Therapeutics</td>
<td>PETX</td>
<td>Kansas City, KS</td>
<td>$6</td>
<td>$10.12</td>
</tr>
<tr>
<td>Esperion Therapeutics</td>
<td>ESPR</td>
<td>Plymouth, MI</td>
<td>$14</td>
<td>$16.90</td>
</tr>
<tr>
<td>OncodMed Pharmaceuticals</td>
<td>OMLD</td>
<td>Redwood City, CA</td>
<td>$17</td>
<td>$26.70</td>
</tr>
</tbody>
</table>

**Figure 10**: Stock prices closed on July 19, 2013.
5.2.4 Corporate Partnerships

Lastly, SironRX has the option of forming a partnership with a large pharmaceutical company. Partnering benefits both entities – smaller biotech companies receive the additional funding required for bringing their drugs closer to market, while large firms expand their drug pipelines. Many blockbuster drugs that provide large revenues for Big Pharma are approaching, or have already reached, the expiration of their patents, so large corporations are looking to make a deal that will ensure their next revenue streams. Such a deal could include a licensing fee, R&D funding, milestone payments, equity purchase, and royalties paid by the corporation.\textsuperscript{223} In the case of Pfizer and Excaliard, an $86 million upfront payment was made to Excaliard’s shareholders, with an additional $230 million payable to Excaliard, contingent upon reaching certain regulatory and revenue milestones.\textsuperscript{224} However, these partnerships also come at a cost. In return for up front payments and future milestone payments, the large corporations gain rights to use the technology developed by the biotech companies.

5.2.5 Recommended Financing for SironRX

Given the different alternatives available to SironRX, completion of Phase II studies with venture capital, followed by a partnership with a large pharmaceutical company seems most appropriate. While a company going public does have say in the price of its IPO, the value is also determined by the state of the current market and the investors buying shares from investment banks.\textsuperscript{225} Because the market is volatile and investors do not necessarily “understand the drug development process,” the issuing company may not reach a valuation it deserves.\textsuperscript{226}
Follow on financing from venture capital will be determined by the outcome of Phase I clinical trials. By meeting endpoints and proving the safety and efficacy of JVS-100 in humans, SironRX will be able to return to its investors for a Series B round of financing to carry out Phase II clinical trials. Drug development beyond Phase II clinical trials requires vast reserves of cash; therefore, a strategic partnership will supply SironRX with the capital needed to fund Phase III trials. During this time, SironRX may have the option of pursuing R&D for other applications of JVS-100, like its use for chronic wounds, made possible by the strategic partnership with a large pharmaceutical company. In doing so, SironRX may secure additional IP that will help the Company grow and enter new markets. This partnership will ultimately determine SironRX’s exit strategy.

5.3 Exit Strategy

How a company is going to exit is an important decision for its investors and managers. Exit strategies for biotech companies typically involve either issuing an IPO or being acquired by a large pharmaceutical company. Figure 11 below describes the stages of development of biopharma companies at the time of being acquired, through a trade sale, by large pharmaceutical companies. In 2012, most biopharma companies were acquired at the level of Phase II clinical trials. The reason for the small number of acquisitions at Phase III clinical trials may be due to the fact that across all therapeutic areas, about 50% of Phase III clinical trials fail, mostly due to lack of efficacy data. There are also many fewer drugs that reach this stage of development.
Figure 11: Stage of product development at time of trade sale.\textsuperscript{229}

Figure 12 below illustrates that large pharmaceutical companies acquire smaller biopharma companies because of a specific product or products that are in development, rather than buying an entire broad platform being developed by the smaller companies.\textsuperscript{230} Big Pharma wants to see specific products in clinical trials that show strong promise of becoming marketed drugs. This bodes well for SironRX, as it is solely focused on developing JVS-100 for a specific market, with clinical trials underway to test its safety and efficacy, putting the Company in a position to be acquired by a large firm.
Because Phase III trials are comprehensive and incur great costs, SironRX should align itself to enter into an acquisition agreement with a large pharmaceutical company. While this will result in the large corporation assuming ownership of SironRX, the acquisition will also supply SironRX with a large upfront payment to finance Phase III trials, with the ability to secure additional financing by meeting milestones throughout the product development timeline. This inflow of cash can continue after commercialization by receiving royalties on the sale of JVS-100.

While recommendations can be made for SironRX to reach commercialization, there are always risks when bringing a new product to market because of the many factors that are simply out of a company’s control. However, by following the aforementioned steps in securing additional financing and establishing an exit strategy, these risks can be reduced.
6. Sales and Distribution Channels

How JVS-100 is sold to customers will depend on how SironRX accomplishes FDA approval of the drug. In one scenario, if SironRX maintains ownership of its technology, it will decide the channel most appropriate for selling JVS-100. The first option is to set up a sales force to sell direct. Broadly speaking, for the purpose of estimating expenses for selling directly to its customers, if SironRX is to target community hospitals, of which there are about 5,000 in the U.S., a sales team of about 100 people would be more than sufficient to capture 20% of that market, or 1,000 hospitals. Considering salaries of the sales people would be about $100k each, it would cost roughly $10M just to pay the sales team. Sales people would not be spread evenly across the U.S., as procedural volumes vary across the country, with more procedures occurring in major cities than in less populated areas.232 By positioning sales teams closer to major cities and hospitals, less personnel would be required to capture the same market size as if sales teams were evenly distributed across the U.S. If SironRX chooses not to sell direct, a second option is for SironRX to partner with a distributor that would sell JVS-100 directly to hospitals.

In the event that SironRX becomes acquired or licenses JVS-100 to a pharmaceutical company, the pharmaceutical company who gains control of the technology becomes responsible for selling the drug. Large firms have the advantage of experienced sales and marketing teams to sell products to customers. As an example of Big Pharma’s budget for marketing, at the high end Pfizer allocates upwards of $600 million for advertising, while at the lower end, Otsuka Pharmaceutical spends about $115 million on marketing.233,234
Whichever route JVS-100 becomes commercialized, hospital administrators have the option of buying through a group purchasing organization, such as Premier. In this case, the owner of JVS-100 would become a contracted supplier to Premier and would have access to nearly 3,000 community hospitals in the Premier network. This would probably be the best option for SironRX because the partnership would grant instant access to a large customer base, albeit at an additional cost to SironRX as it would likely need to discount the drug price in exchange for access to the group purchasing organization.

In any instance, there must be an economic incentive for a hospital or doctor to buy a drug. When choosing the best option for treating their patients, physicians also consider the cost implications of their decisions. In a survey by Bain & Company, about 80% of doctors agreed that among their duties was the responsibility to lower healthcare costs for their patients. Regarding SironRX, there is an economic incentive to using its drug, as it is a one-time preventative therapy that can cut costs for both hospitals and patients, as discussed previously.

7. Projected Financials at Commercialization

While projecting revenue for a new drug product is a complicated process with many variables, an attempt will be made to construct a general idea of what revenues may look like for a drug like JVS-100 once it reaches the market. This process is further complicated by the fact that JVS-100 is only in Phase 1 clinical trials and it will be at
least seven to eight years before it reaches commercialization, provided that later stage clinical trials are successful.

L.E.K. Consulting has devised a formula to estimate the revenue of a new product entering the market. The formula consists of five variables: customer base, total market penetration, the product’s share of market penetration, price per unit, and units per year. The following is an exercise using this formula to estimate revenue from JVS-100 once it becomes commercialized.

Generally speaking, two types of customer bases exist: a customer base consisting of buyers who purchase a product or service on a recurring basis, or “prevalence,” and those who purchase a product or service on a one-time basis, or “incidence.” SironRX’s customers can be described as an incidence customer base, as they will be receiving a one-time injection of JVS-100 after surgery. Another facet of the customer base is determining the specific customer segment a product will most likely serve. While there are about 50 million inpatient procedures and over 20 million procedures performed in ambulatory surgery centers (ASCs) every year in the United States, not all of these procedures are appropriate for the use of JVS-100. Some of these procedures do not require incisions; therefore, this is no scar to prevent from forming or wound to heal rapidly. Of the roughly 70 million procedures performed in inpatient settings and ASCs, if only half required a dermal incision, 35 million procedures could benefit from the use of JVS-100. This number can change over time, depending on the total number of surgeries performed in a year.
The next variable to consider is total market penetration. This variable is estimated by determining how many customers in the customer base use products similar to the new product entering the market. In this case, it would be treatments used for scar reduction. Total market penetration is affected by how well current treatments meet the needs of patients. Because current scar treatments do not work to prevent the formation of scars, an unmet need exists for a prophylactic treatment. However, in order to estimate total market penetration, as there is limited data on the percentage of patients that seek scar treatment after surgery, one can look at a survey published in 2009 that reported about half of the patients attempted to conceal their scars who acquired them after undergoing surgery. Therefore, 17.5 million patients (half of the 35 million procedures that could benefit from JVS-100) represent the total U.S. market penetration for anti-scarring products.

After evaluating the total market penetration, it is necessary to estimate the product’s share of market penetration. In doing so, three factors come into play:

1. Determining the peak market share of a product. This can be done by comparing the characteristics of the product to be introduced in the market with those of the competitors. This can include such things as the product’s formulation, indication, efficacy, safety, and price. Based on these factors, as mentioned earlier regarding SironRX’s benefits per costs and position relative to its competition, it is estimated that SironRX will reach a peak market share of 10%, or 1,750,000 procedures annually.
2. Determining the “ramp-up” of a new product’s sales to the peak market share. In the pharmaceutical industry, how fast sales reach the peak market share depends on a number of factors, including physician, patient, and payer (insurance carrier) acceptance of the product, sales and marketing strategies, and post-market studies (Phase IV clinical trials). For a drug like JVS-100, it is estimated that it will take five years to reach peak market share.

3. Determining the “ramping-down” of product sales, which for SironRX would be affected by new competitors entering the market and expiration of its patent. As there currently are few potential strong competitors for SironRX, and its patents are relatively new, SironRX will experience a sustained, large market share.

The last two components when estimating revenue are price per unit and units per year. SironRX can estimate the price of a round of injections after surgery to be about $1,500 as discussed previously. Units per year are affected by the “frequency of use” and “compliance by the end user” of the product. It is most likely that patients will receive only one round of injections, and a physician will administer the injections; therefore, compliance by the end user does not come into play.

Using this framework, the following revenue forecast has been made for JVS-100, which is shown in Figure 13 below, from its time in clinical trials to market launch and beyond.
Conclusion

Based on its value proposition and an evaluation of its position among its competitors, SironRX will be a strong contender in the wound healing and scar therapy market. While the current focus for SironRX is strictly acute surgical wounds, the Company can explore other sectors including chronic wounds, like diabetic foot ulcers, and devices, like smart bandages, through a partnership with a medical device manufacturer. However, the current focus of SironRX should be to complete Phase I clinical trials and present the outcomes to its investors to secure additional financing for Phase II trials. Completion of Phase II trials and a demonstration of the efficacy and safety of JVS-100 will allow SironRX to form a strategic partnership with a large pharmaceutical company to carry out Phase III studies. As these late stage clinical trials ultimately determine if the FDA will approve JVS-100, SironRX and its partner must design and implement studies that best
take advantage of their resources. This strategic partnership will extend to the sales and distribution of JVS-100 to gain a considerable market share. The financial forecasts made in this paper are broad estimations based on the current and future market and serve to give a general sense of the revenue that could be realized through sales of JVS-100.
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