US clinical trial puts Sernova one step closer to diabetes cure

As a general rule, the most successful man in life is the man who has the best information

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Last week I read a shocking post on one of my social media feeds. The author was a diabetic who displayed a photo of a bill from Walgreens and two boxes of insulin. Three vials of Humalog cost the man $807.96, which lasts one month. At that rate, his annual insulin tab is just under US$10,000 a year, and this is with health insurance coverage. He calculated the price of insulin has been marked up 500% since it was first introduced in the 1920s. "It's insulin, not tiger blood. This is BS and needs to change," reads the post from the man who lives in North Carolina. It ends with the hashtag #LiquidGold.

Patients who have been diagnosed with diabetes, Type 1 or Type 2 (about 30% who take insulin) not only have to contend with the high cost of insulin which in the US is onerous, but the daily ritual of injecting themselves with insulin to control their blood sugar levels. People with diabetes must carefully monitor their blood sugar throughout the day and take multiple doses of insulin based on food intake, exercise, stress, illness, etc. A miscalculation or unexpected variable leading to high or low blood sugar levels are daily threats leading to accumulating long term consequences. Only about a third of Type 1 diabetics achieve their long- term glucose targets.

Insulin injections take the place of natural insulin which is normally produced by islets in the pancreas. Those with Type 1 diabetes have a condition whereby the pancreas does not make enough of the hormone insulin, while Type 2 diabetics' blood sugar level is too high because the body doesn't produce or use insulin normally. Over time, people with either condition can develop serious complications including heart disease, strokes, kidney problems, nerve damage and eye problems.

But what if the cells (islets) that release insulin could be transplanted into the body within an implantable delivery mechanism, allowing the body to

produce natural insulin? Such a device would render insulin injections unnecessary, thereby vastly improving the lives of people with diabetes.

That is the goal of Sernova Corporation (TSXV:SVA; OTCQB: SEOVF; FSE: PSH), a London, Ontario-based company which in December was granted IND clearance by US Federal Drug Administration (FDA) to conduct a human clinical trial for its Cell Pouch technologies, designed to treat diabetes, hemophilia and thyroid disease.

The Cell Pouch

The diabetes trial is a major milestone for Sernova, which has been developing the Cell Pouch since 2009. The device is essentially an implanted housing vehicle for therapeutic cells that produce and deliver insulin, as needed. The cells, which can either be stem cell derived or sourced from organ donors, are implanted into the Cell Pouch to produce proteins or hormones that are in short supply or missing from the body, a result of the disease the patient is suffering from.

About the size of a credit card, the Cell Pouch is surgically implanted under the skin, where it creates an "organ-like" environment that allows the therapeutic cells to integrate within the body. The surgery can be a simple outpatient procedure.

Sernova's President and CEO, Dr. Philip Toleikis and his team early on realized they needed to create an environment that incorporates tissues and blood vessels rather than "walling them off" which is what usually happens when a medical device is implanted in the body becoming surrounded by scar tissue, a process known as fibrosis. The scar tissue could trap the therapeutic cells, preventing them from integrating with the rest of the body, and they eventually die.

Sernova's Cell Pouch™ forms a natural vascularized environment for long-term survival and function of the therapeutic cells which release into the bloodstream requiring but missing proteins or hormones like insulin.

The technology would be beneficial if it provided a simple reduction in the number of insulin injections a patient must take; however, there is the possibility that it could even essentially 'cure' the disease through natural release and regulation of insulin.

The Cell Pouch is also an ideal delivery vehicle for cells which produce factor VIII, a blood-clotting protein absent in patients with hemophilia and thyroid

cells which produce thyroid hormones that are in short supply in patients with thyroid disease.

Sernova has shown its technology to be safe and effective in multiple small and large animal preclinical trials, and it has also been proven in a first in human clinical trial in Canada which demonstrated safety of the device, survival of human islets (a grouping of therapeutic cells) and the presence of insulin from islets implanted under the skin within the Cell Pouch - a world's first.

"We believe the Cell Pouch platform is the first such patented technology proven to become incorporated with blood vessel enriched tissue-forming tissue chambers without fibrosis for the placement and long-term survival and function of immune protected therapeutic cells," Sernova stated in a July 24th, 2017 news release.

"The important point is that we designed the device early on to create a natural and ideal tissue environment for all therapeutic cells. Sernova's technologies form a platform technology for potential treatment of multiple diseases," Toleikis told Ahead of the Herd in a recent interview. He stressed that Sernova is likely two or more years ahead of other regenerative medicine companies trying to do similar work, a number of which have been unable to clear the fibrosis hurdle that Sernova has cleared.

"We have definitively shown two critical points with all of our preclinical studies and with human islets in humans. First, our Cell Pouch can keep human islets alive and highly vascularized. And the other thing that we have shown in a year-long study is that our device does not fibrose," added Toleikis, who studied different combinations of drugs and medical devices to improve the functioning of the latter while Vice President of R&D, Pharmacology and Drug Screening when he was at Angiotech Pharmaceuticals which developed one of the first drug-eluting coronary stents, a multi-billion dollar technology.

"We believe we are the first company to show that human islets can survive and become vascularized within a tissue matrix housed in a medical device that's implanted under the skin."

The trial

The next step for Sernova was to get approval from the US Federal Drug Administration (FDA) to conduct a human clinical trial for a group of patients in the United States, utilizing the Cell Pouch. On December 11, 2017 Sernova announced it had been granted a notice of allowance from the FDA

for a new clinical trial using patients with Type 1 diabetes that have hypoglycemia unawareness.

Hypoglycemia unawareness is a complication of diabetes whereby the patient is unaware of a deep drop in blood sugar levels because the body fails to trigger a secretion of epinephrine, which generates symptoms of hypoglycemia such as palpitations, sweating and anxiety. The condition can result in prolonged exposure to hypoglycemia, resulting in a seizure, loss of consciousness or brain damage. It's estimated that around 30% of diabetics have hypoglycemia unawareness.

The company-sponsored trial is to investigate the ongoing safety as well as efficacy of the Cell Pouch with a yet-to-be-released number of hypoglycemia unaware patients. The patients will have the Cell Pouch implanted, with the first objective being to assess the safety and tolerability of islet transplantation into the Cell Pouch, and secondly, the efficacy of the treatment. The patients' progress will be tracked for about six months, after which a decision will be made whether to transplant a second dose of islets. Those patients will then be further followed for a year. Thus, the trial enables understanding of the effects of potential multiple doses of cells within the Cell Pouch.

The trial is being backed by a significant grant from the Juvenile Diabetes Foundation - the world's largest supporter of diabetes research. The grant went through a six-month due diligence process, including high-level academic reviews, and is an important validation of the company's research, said Toleikis.

"The review process involved peer review of the clinical protocol, and receipt of the support indicated that the study is considered important, that the indication of hypoglycemia unawareness is an important unmet need in these patients and that the Cell Pouch preclinical data is strong," he said.

Key attributes of the new trial include refined surgical techniques involved in implanting the Cell Pouch, means to ensure high quality and purity of the islets, controlled dosing of islets, taking multiple measures of efficacy and assessment of several potential doses of cells to understand the effect of islet dosing.

The Holy Grail for diabetes?

Toleikis sees the trial for hypoglycemia unaware patients as the first pool of patients using the Cell Pouch that if successful could eventually mean expanded trials in Type 1 as well as Type 2 patients, a market that

represents up to 60 million patients worldwide. This is especially true if stem cell derived technologies - which are cells that can differentiate into specialized glucose responsive insulin producing cells - are implanted into the Cell Pouch as an unlimited supply of cells as Sernova's technologies advance.

While not widely publicized, Sernova has obtained a world-wide exclusive license for a stem cell derived technology developed by luminaries Drs. Gordon Keller and Cristina Nostro for the treatment of diabetes through the University Health Network, a Toronto-based medical research organization. The ability to use stem cells is important for Sernova because it means the company would eventually not have to rely on organ donors for obtaining therapeutic cells; moreover, stem cells are considered to be easier to implant and more survivable than pancreas-derived islets.

"The hypoglycemia unawareness market itself is a significant market in the United States, but we are also working on unlimited supplies of cells such as a stem cell-derived technology that can then go into the Cell Pouch. If successful, that particular technology may be used to treat the general population of diabetic patients," said Toleikis.

"We see our Cell Pouch technology with human donor islets as an importantl indication to help hypoglycemia unaware patients, but we also see that indication and validation as a launch pad supporting our work with other types of cell technologies such as the glucose responsive insulin-producing stem cell technologies or even encapsulated porcine [pig] technologies."

Further details of the study will be made public when institutional ethics board (IRB) review is completed, a process which occurs at the clinical sites following FDA clearance. At its technologies advance, Sernova plans to conduct trials with several of its diabetes technologies: the first will have the patients take donor islets protected by immunosuppressive drugs which help the islets to survive in the body. A second, separate later anticipated trial (not yet approved) expects to involve patients who have the Cell Pouch implanted but do not take immunosuppressive drugs. Those patients will have Cell Pouches equipped with therapeutic cells that provide local immune protection to reduce or eliminate the need for anti-rejection drugs. If the second trial is proven effective, Sernova may have a practical 'cure' for diabetes.

"For the larger patient population with diabetes who may not have severe hypoglycemia unawareness, our goal is to develop a product where patients will receive locally immune protected cells within the Cell Pouch that will produce insulin and all the hormones as required to control blood sugar

levels," said Toleikis. "This is the Holy Grail of diabetes treatment – to free these individuals from constant worry."

What it means for individuals with diabetes

Diabetic patients could see a considerable improvement in their quality of life should the Cell Pouch technologies continue to prove to be safe and to show efficacy in clinical trials.

"We're anticipating that with appropriate islet dosing, a period after the islets are transplanted into the Cell Pouch and become vascularized, they will start to function, releasing insulin to take over glucose control as the patients reduce their insulin doses," said Toleikis. "The end goal is that the islets begin to control blood sugar levels and the injections tapered down to the point where they are no longer necessary."

If that were to happen and the sugar levels were controlled in a normal way, these individuals may also benefit from a reduction of accumulating microvascular side effects of diabetes, which include eye, kidney and nerve damage, as well as heart attack, stroke and amputations.

"That would be ground-breaking - a highly disruptive, significant improvement in the quality of life of those patients," said Toleikis, adding that "a de facto 'cure' for diabetes could significantly reduce hospitalizations and worldwide healthcare costs that are becoming a significant burden for worldwide government healthcare budgets."

"We anticipate that if regenerative medicine products prove out as we continue to move forward, they will be the largest medical products ever in the history of medicine to treat patients and, likely, one of the most significant achievements in therapeutic treatment of disease in improving the quality of life of millions of patients."
The timeline

Asked how long it could be between getting the first patient enrolled in the clinical trial, conducting this and other trials needed for regulatory approval for marketing approval of the first product, Toleikis said the exact timeline depends on many factors but gave an estimate of three-four years or so depending on the outcome of the trial and regulatory requirements. For these hypoglycemia unawareness patients, if the results show significant benefit, the company has the potential to apply for fast track status for the therapy in this population.

Toleikis noted the company is interacting with pharmaceutical companies that have stem cell technologies and overall interest in regenerative medicine that could dovetail with the Cell Pouch delivery system. Virtually every major pharma company such as Merck, Takeda, Novo Nordisk, and Sanofi have publicly shown strong interest in the new wave of regenerative medicine therapeutics, an indication that regenerative medicine is being taken very seriously.

"Sernova can be considered the hub of the wheel if not the entire wheel of the processes that are going on for regenerative medicine requiring replacement of proteins or hormones in the body. We are bringing all the pieces of the regenerative medicine puzzle together including the prevascularized device, the therapeutic cells and local immune protection of the cells. We want to work with pharma and medical device companies in the development and marketing of our products and are actively seeking collaborations," said Toleikis. "If one thinks about it, medtech companies are experts in devices and may not have cell therapy experience and pharmaceutical companies may not have medical device experience. Sernova's expertise crosses both arenas but we don't yet have the ability to market the products or the deep pockets for the pivotal trials. This mutual need makes a collaboration between Sernova and these companies a potential 'marriage made in heaven" in a win-win relationship towards commercialization of these multi-billion dollar products."

A cure for hemophilia?

Sernova has not only made startling progress lately with respect to a potential 'cure' for diabetes, it has also made great strides in its other main product development arena, hemophilia.

Sernova is a member of the Horizon 2020 granted HemAcure consortium which has united academic institutions from Germany, Italy and the UK with Sernova's corporate experience and mission in developing a product to treat hemophilia A patients with a cell therapy product within the Cell Pouch.

The overall objective of the HemAcure project is to develop and refine the tools and technologies for a novel, curative ex vivo (outside the body) gene therapy in cells placed in the implanted Cell Pouch to treat hemophilia A that could ultimately lead to improved quality of life for patients. The EU's Horizon 2020 program has funded the HemAcure project with €5.6 million (approximately CAD$8.06M, US$6.3M). The most recent tranche of funding was cleared in July, 2017 based on the encouraging mid-term results reported to the European Union. In addition to the JDRF grant, receipt of the

highly prestigious Horizon 2020 grant is a strong validation of Sernova's technologies.

Sernova's goal is to do the same thing for patients with hemophilia as for diabetic patients, in clinical trials using the Cell Pouch.

"With the HemAcure team we are working on a product repairing the patient's own cells, called an autograft therapy." Toleikis explained. "We take a blood sample from the patient. We then isolate a certain cell type called an endothelial cell and insert the gene for factor VIII so those cells start to produce factor VIII. We can then expand or multiply those cells and transplant them into the Cell Pouch that's under the skin. The idea is for those cells to produce factor VIII on a constant basis which becomes therapeutic when it enters the bloodstream."
Having a sufficient amount of factor VIII constantly released into the bloodstream can significantly reduce the symptoms of hemophilia, which include heavy bleeding from minor cuts and more seriously, internal hemorrhaging that can take place in joints (especially knees, ankles and elbows) and into tissues and muscles. Bleeding can also occur in vital organs putting a patient's life in danger.

Although effective treatment of the symptoms is available through frequent infusions, there is no cure for hemophilia A at present and therapy has to be individualized to each patient. Currently patients require lifelong infusions with factor VIII several times a week to compensate for the missing clotting factor.

The global total hemophilia market was valued at US$9.3 billion in 2015. Approximately 20,000 people in the United States, 10,000 in Europe and approximately 2,500 in Canada have a moderate or severe form of hemophilia A. Annual costs for the treatment of the disease for each patient may range from $60,000 to $260,000 for a total cost of between $2-5B per year just in North America and Europe.

Derisking

A regenerative medicine company like Sernova is in a way similar to a resource company in that the valuation of the company and its stock price is intimately tied to de-risking. In Sernova's case, this derisking comes from multiple sources. One is about working on multiple products. Sernova has three diabetes products, one current hemophilia product and a thyroid disease treatment product in its pipeline. The other derisking approach Sernova has taken is its interest in cutting deals with pharma and medtech companies to help advance its programs to commercialization status.

Meeting milestones in its product development pipeline as well as initiating collaborations with corporate partners are each expected to contribute in a major way to the company's valuation.

"I am very excited about 2018 and the coming years," said Toleikis. "We have spend years building the foundation of our technologies and it is starting to show in a big way. We have validated our technologies in major preclinical studies, and have demonstrated first in human safety and survival of cells within the Cell Pouch. We have proven that the Cell Pouch is a viable device for cell survival and are now aggressively moving forward in US clinical trials with confidence."

Conclusion

Investors in Sernova have been patiently waiting as the company has developed and tested their regenerative medicine products. I believe that investor patience is finally being rewarded as Sernova proves its technologies are safe and effective, with results that could be life-changing for diabetics, hemophiliacs and any other patients requiring therapeutic cell transplants.

We believe Sernova is the only company in this space with the combination of technologies to enable 'cures' to these serious diseases. Where other companies are concentrating on the "payload" (cells) that get implanted into the body, Sernova has the only known delivery device that prevents fibrosis - this is the key to ensuring that the therapeutic cells survive and do their work. Sernova's success could represent a true medical breakthrough. How many companies can that be said about? For these reasons Sernova is on my radar screen. Is SVA on yours?

If not, it should be.

Richard (Rick) Mills
aheadoftheherd.com

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