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Islet Cell Replacement Therapy for Insulin-Dependent Diabetes



Image courtesy of ViaCyte

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Summary

- ViaCyte’s PEC-Direct and PEC-Encap (VC-01) products offer a potential “functional cure” for patients with type 1 diabetes and insulin-dependent type 2 diabetes.
- Using human pancreatic progenitor cells (PEC-01) created in the lab, both the PEC-Direct and the PEC-Encap products are implanted into patients, where they mature into functional pancreatic islet tissue that includes glucose-responsive insulin-producing beta cells.
- The PEC-Encap product offers the additional benefit of an encapsulation device designed to protect the cells from the immune system.
- The current evidence is limited to phase I and II human trials evaluating the safety of the PEC-Encap product and pre-clinical study of the PEC-Direct product.
- There are insufficient data about efficacy in humans, adverse effects, and the length of time the product can remain safely implanted and functional.
- The future cost of ViaCyte’s products is unknown.

Issue

Islet cells are the cells in the pancreas that are responsible for insulin production.¹ In type 1 diabetes, these cells are destroyed by the immune system.¹ For people living with type 2 diabetes, the body becomes resistant to the insulin it produces, does not produce enough insulin, or may experience a combination of both insulin resistance and insufficient insulin production.²

Islet cell replacement therapy involves placing new islet cells into a person’s body to better control their blood sugar levels and to potentially serve as a functional cure for their diabetes.¹ There are a variety of procedures in which patients can receive new islet cells.¹

The first major success in islet cell replacement therapy for insulin-dependent diabetes was published in the year 2000 as the Edmonton Protocol, in which purified islets from cadaver pancreases were isolated and cryopreserved (a process that keeps cells and other biological material alive by cooling them to very low temperatures) and then transplanted into people with type 1 diabetes. The patients no longer needed insulin.^{3,4} While the success of this procedure generated much excitement among researchers in the field, key limitations of islet transplants

from cadavers were the severe shortage of donor cells and the need for lifelong immunosuppression to prevent the recipient’s immune system from rejecting the transplanted cells.^{3,8}

One company, ViaCyte (San Diego, California), is currently developing islet cell replacement therapies that may prove capable of overcoming both of these limitations.³

The Technology

ViaCyte’s PEC-Direct and PEC-Encap product candidates are in the pre-clinical and clinical stages, respectively.³ Both products use human embryonic stem cells to create proprietary pancreatic progenitor cells (PEC-01 cells, which are cells that have started the process of becoming islet cells), in the lab.³

ViaCyte’s products may resolve the shortage of available cells for transplant by creating a virtually limitless supply of PEC-01 cells in the lab, which can then be implanted into the body. The need for lifelong immunosuppression is addressed by ViaCyte’s PEC-Encap product candidate, which encloses the transplanted cells in a unique encapsulation device that may help protect them from the immune system.^{3,5}

The PEC-Direct Product

The PEC-Direct product contains PEC-01 cells; it is surgically implanted under the skin during an outpatient procedure.⁹ Due to the auto-immune nature of type 1 diabetes, as well as the fact that these cells are allogeneic (genetically similar but not identical), patients are expected to require immunosuppression for the rest of their lives.^{3,4}

The risks of lifelong immunosuppression include an increased risk of infections and cancer, as well as the potential for the immunosuppressive drugs to negatively affect islet function.^{4,7} Because of these risks, ViaCyte plans to use the PEC-Direct product only in people with high-risk type 1 diabetes, defined as those who experience:

- impaired awareness of low blood sugar levels (hypoglycemia unawareness)
- extreme fluctuations of blood sugar (glycemic lability) and/or
- frequent and severe incidences of low blood sugar (hypoglycemic episodes).³

The PEC-Encap (VC-01) Product

ViaCyte's PEC-Encap product uses the same PEC-01 cells as the PEC-Direct product, and it is also implanted under the skin during an outpatient procedure.^{3,10} However, the PEC-Encap product takes the PEC-Direct technology one step further by enclosing the cells in a semi-permeable encapsulation device. The device – called the Encaptra drug delivery system – is hypothesized to prevent the need for immunosuppression.^{3,7,9-11} The PEC-Encap product is intended for all people living with type 1 diabetes as well as for those living with insulin-dependent type 2 diabetes.

The PEC-Encap (VC-01) product is about half the size of a business card (EN250 model) (Figure 1).^{10,12} However, for the purposes of clinical trials, a smaller version that is about the size of a dime – the EN20 sentinel – has been created to allow for closer monitoring, analysis, and troubleshooting during clinical trials.¹²

Figure 1: The PEC-Encap (VC-01) Product Candidate

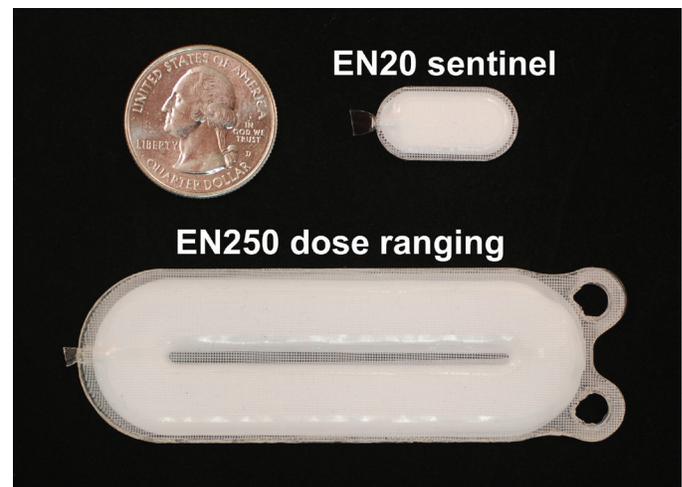


Image courtesy of ViaCyte

The goal of the PEC-Encap product is to optimize the exchange of key nutrients (such as glucose and oxygen) and key therapeutic outputs (such as insulin), while simultaneously protecting the implanted cells from the immune system.^{3,10,13}

Prior to the PEC-Encap product, researchers in the field of islet encapsulation tried for more than 40 years to create an effective encapsulation device without success.^{7,13} It is possible that ViaCyte will be the first to achieve this feat, which could change the landscape of diabetes management.

Proposed Therapeutic Benefits

The proposed therapeutic benefits of ViaCyte's PEC-Direct and PEC-Encap products are:

- normal blood glucose (blood sugar) levels, thus preventing the acute and chronic health complications of diabetes (PEC-Direct and PEC-Encap).
- elimination of the need for ongoing glucose monitoring (PEC-Direct and PEC-Encap).
- elimination of the need for immunosuppression (PEC-Encap).^{3,14,15}

Availability

The PEC-Direct and PEC-Encap (VC-01) product candidates are not approved for use outside of a clinical trial in Canada or elsewhere.

The PEC-Direct product is still in the pre-clinical (animal model) phase of research and is expected to reach the clinical phase in 2017.³ The PEC-Encap product is currently in phase I and II clinical trials that began in 2014 to evaluate its safety and efficacy.^{3,16}

The PEC-Encap product was approved by the FDA in 2014 when the STEP ONE trial began in San Diego.^{9,16} The product was subsequently approved for clinical testing by Health Canada and, in July 2015, the STEP ONE trial was expanded to include its first Canadian site at the University of Alberta Hospital in Edmonton.^{9,16}

Neither the PEC-Direct nor the PEC-Encap products are expected to be available outside of clinical trials for several years.^{3,17,18}

Cost

The cost of the PEC-Direct and PEC-Encap products is not yet known.

Who might benefit?

ViaCyte's PEC-Direct product is intended only for patients living with high-risk type 1 diabetes (also called "brittle" or "labile" diabetes).^{3,19} Between 10% and 15% of the approximately 350,000 Canadians living with type 1 diabetes^{20,21} are considered "high-risk" due to severe problems with hypoglycemia (low blood sugar) that are debilitating and can lead to serious complications, including coma and death.^{3,19}

In these high-risk individuals, the potential benefits of the PEC-Direct product candidate — including insulin independence, normal glucose levels, and elimination of dangerous complications that could lead to hospitalization or death — are expected to outweigh the risks.³

ViaCyte's PEC-Encap product hopes to target all people living with type 1 diabetes as well as all people with insulin-dependent type 2 diabetes, making it available to a much broader range of patients.³

Current Practice

The treatment for type 1 diabetes is lifelong insulin therapy combined with regular blood glucose monitoring.^{15,22} Insulin must be carefully administered to match an individual's needs, and must take into account diet and physical activity.²² Insulin can be delivered by either multiple daily injections, or using an insulin pump (continuous subcutaneous insulin infusion).^{13,22}

The treatment for type 2 diabetes starts with lifestyle recommendations such as appropriate exercise, a healthy diet, and smoking cessation, all of which contribute to better glucose control.^{23,24} According to the US Centers for Disease Control and Prevention, 63.3% of people living with type 2 diabetes also require medications to manage their condition.²³⁻²⁵ Metformin is the most frequently used first-line treatment, and additional medications can be added as needed to optimize glucose control.²⁴ Appropriate medical management of cardiovascular risk factors including optimizing blood pressure and cholesterol is also key, and individuals should receive regular screening for diabetes complications.²²⁻²⁴

Some people with type 2 diabetes may also require insulin therapy to better control their blood sugar levels as the disease becomes more severe.^{22,24} Insulin is typically considered only after lifestyle modifications and medical management have failed to provide adequate glucose control.²⁴ For people living with type 2 diabetes, insulin is most frequently used in combination with medical management.^{22,24}

The Evidence

There are currently only two phase I and II clinical trials underway, both assessing the PEC-Encap (VC-01) combination product in humans.^{17,18} The PEC-Direct product is still in pre-clinical phases of research that will not be covered in this bulletin.³

The First PEC-Encap Trial (STEP ONE)

The Safety, Tolerability, and Efficacy of Various Doses of VC-01 Combination Product in Subjects With Type 1 Diabetes Mellitus (STEP ONE) clinical trial for the PEC-Encap product (VC-01) began in the US in 2014. It was subsequently expanded to its first Canadian site at the University of Alberta Hospital in Edmonton in July 2015.^{3,9,18} It is a cohort study sponsored by the manufacturer, ViaCyte.^{11,18}

The STEP ONE trial consists of two patient groups who are scheduled to receive the PEC-Encap (VC-01) product at increasing doses, provided no safety concerns arise.⁹ Patients in the first group are receiving a sub-therapeutic dose of two VC-01 implants.¹⁸ The goal for this patient group is to evaluate the safety of the device at sub-therapeutic levels, to ensure that the Encaptra device is an effective barrier to the immune system, and to assess the optimum location of implantation.⁹

Assuming that the first stage of the STEP ONE trial is successful and that there are no safety concerns, a second group of patients will receive four or six VC-01 implants.^{9,18} The goal with the second patient group is to evaluate both the safety of the product as well as its effectiveness at increased doses.⁹ C-peptide levels will also be evaluated to indirectly measure insulin secretion from the newly implanted beta cells – an indication the cells are working. This will give researchers insight into the dose of VC-01 product needed to achieve insulin independence.^{3,18,26}

“There are currently only two phase I and II clinical trials underway, both assessing the PEC-Encap (VC-01) combination product in humans.”

The projected completion date for the primary outcome measure in the STEP ONE trial is August 2017.¹⁸

One issue reported by STEP ONE researchers is a fibrotic immune reaction (scarring) on the outside of the PEC-Encap device, causing many of the cells to die within a few months of being implanted.⁷ In a December 2016 *Nature Review*, Paul Laikind, ViaCyte’s chief executive, stated that the company will focus on modifying the encapsulation device (or other procedural aspects of administration) to address this issue.⁷

The Second PEC-Encap Trial – Three-Year Follow-Up

A second trial of the PEC-Encap product began in October 2016.¹⁷ Patients previously implanted with a VC-01 combination product are enrolled by invitation as they have their last PEC-Encap units removed and complete the STEP ONE trial.¹⁷

The purpose of this second trial is to evaluate the long-term safety of the VC-01 combination product.¹⁷ This manufacturer-sponsored cohort study has a projected completion date of November 2023.¹⁷

Safety

There is currently little information about the clinical safety of either the PEC-Direct or the PEC-Encap products.¹⁸ This is because the PEC-Direct product is still in pre-clinical phases, and the PEC-Encap product only recently began phase I and II testing in humans.^{17,18}

In clinical trials to date, there have been no significant safety concerns reported with ViaCyte’s PEC-Encap (VC-01) product.³ Most of the adverse effects for the PEC-Encap product in the STEP ONE trial have been those expected from an outpatient surgical procedure – post-operative discomfort following implantation of the device, as well as the potential for bleeding, inflammation, or infection at the site of the wound.^{3,27} Further information regarding safety of the PEC-Encap product will be available upon completion of the clinical trials.

Both the PEC-Direct and PEC-Encap products use a macrodevice design that allows for easier viewing of the device using imaging techniques and easier removal should the need arise. The design may also offer potential safety benefits.^{3,10,13}

Cost-Effectiveness

Results of a 2012 cost-effectiveness study conducted by the University of York supported islet cell transplantation as a more cost-effective option than insulin therapy for people with high-risk type 1 diabetes after nine to 10 years.²⁸ Islet cell transplantation had a projected 20-year cost of US\$519,000, while insulin therapy had a projected 20-year cost of US\$663,000.²⁸

Concurrent Developments

ViaCyte recently obtained proprietary rights for all of the assets from its primary competitor, BetaLogics.^{7,11} However, while ViaCyte is one of the leaders in the field, other research has also been in the works.⁸

Scientists are exploring a variety of approaches to supply functional beta cells for patients with insulin-dependent diabetes.⁸ In addition to stem cell therapies, the other major approach currently being studied uses cells from elsewhere in the pancreas (pancreatic non-endocrine cells) and reprograms them (by directed differentiation) to become beta cells.⁸

Researchers are also looking into a variety of different encapsulation strategies.⁵ Microdevices have the advantages of better vascularization (blood vessel growth and availability) and diffusion of key nutrients and therapeutic outputs. However, macrodevices have the advantages of easier implantation, easier location of the product for follow-up and possible removal, and the requirement for fewer products to be implanted (as opposed to the thousands of microdevices that must be implanted to achieve the same number of total islet cells).⁵

Continued research is under way to determine the best strategies for both the beta cell component as well as the encapsulation component.^{5,8} However, ViaCyte's PEC-Encap (VC-01) product is currently the only combination product candidate being tested in phase I and II clinical trials in humans. Nothing else has progressed beyond the stages of animal or laboratory testing.

Implementation Issues

The STEP ONE trial is currently evaluating the optimum procedural techniques and ideal location for implantation of the PEC-Encap units.^{3,18} Both the PEC-Direct and PEC-Encap products are intended to be easily retrievable and easily removed if needed.³ The frequency of administration of the devices, as well as the therapeutic doses and how long they remain effective for, is yet to be determined.

Because using embryonic stem cells involves the destruction of human embryos, some people have ethical concerns regarding their use in regenerative medicine.²⁹⁻³¹ Should ViaCyte's PEC-Direct and PEC-Encap products prove to be safe and effective, the religious and moral beliefs of people who may benefit from the treatment would need to be considered prior to treatment.

Final Remarks

ViaCyte's PEC-Direct and PEC-Encap products still need to complete pre-clinical and clinical phases of testing.^{3,17,18}

At the current stage of research many questions remain, including those regarding product safety, efficacy in relationship to the goal of insulin independence, and how long the products can remain implanted and functional.

Methods — Literature Search Strategy

A peer-reviewed literature search was conducted using the following bibliographic databases: PubMed, MEDLINE, Embase, and the Cochrane Library. Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (www.cadth.ca/grey-matters). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2012, and January 25, 2017. Conference abstracts published between January 1, 2015, and January 25, 2017, were included in the search results. Regular alerts updated the search until project completion; only citations retrieved before February 10, 2017 were incorporated into the analysis.

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