VIACYTE™

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August 21, 2016

Re: CIRM Grant Application CLIN2-08839

Clinical evaluation of improved configurations of the delivery device component of an islet cell replacement therapy for type 1 diabetes

Review date: July 26, 2016

Dear Ms. Bonneville and Members of the ICOC,

Thank you for considering our grant application entitled "Clinical evaluation of improved configurations of the delivery device component of an islet cell replacement therapy for type 1 diabetes". As allowed under the CIRM guidelines, and recognizing that the present recommendation from CIRM is not consistent with that of the Grants Working Group, we are sending this communication to provide additional context, perspective, and information that could help remove ambiguity associated with this situation.

Overview of progress developing the PEC-EnCap product:
The proposed VC01-102 clinical study brought before the ICOC continues the important work that ViaCyte and CIRM are doing together to deliver a potential functional cure for patients with type 1 diabetes. The PEC-EnCap (also known as VC-01) combination product candidate delivers replacement human insulin-producing beta and other islet cells in a packet placed under the skin. The PEC-01 cells delivered in the packet, which is known as the Encaptra device, are manufactured from embryonic stem cells, and thus development of this product candidate fits squarely in the mission of CIRM.

With CIRM's tremendous support, starting with a basic research-level project, we have made great advances in the field and have moved the product candidate through pre-clinical and now into clinical testing. The clinical investigation of PEC-EnCap has been underway for almost two years, and in that time we have collected a great deal of insight on how to translate the product for human application.

Not surprisingly, with this largely unprecedented groundbreaking work we have been learning along the way, and we have been modifying the product and procedures in real time to improve the implementation of PEC-EnCap. The current proposal continues these efforts by generating critical human trial data to help us optimize the device component of PEC-EnCap. We feel that the planned modifications to the Encaptra device may make a significant difference in how the body interacts with the product, and therefore how well the product engrafts and functions. Success in this clinical trial could relieve a bottleneck in PEC-EnCap development, and in the regenerative medicine field of macroencapsulation generally.

When an object, such as the PEC-EnCap product candidate, is placed under the skin, there is a naturally occurring foreign body response (FBR). As a subcutaneous implant, PEC-EnCap must work within the context of, even take advantage of, the biology of the FBR in order to engraft into the patient's body. Engraftment includes survival and maturation of the implanted PEC-01 cells, and vascularization of the PEC-EnCap units. The incorporation of the product into the body's blood circulatory system, and development of glucose-responsive insulin producing cells, is the key to PEC-EnCap function.

While the team has been making progress in improving product engraftment in patients with type 1 diabetes additional improvements are needed. The proposed clinical study is designed to evaluate four new device configurations that we believe could substantially improve engraftment, including interaction with the biology of the FBR in human tissue. The fact that this study can be performed in human subjects is critical. Because of differences between humans and other species in immune function, tissue characteristics, and other important variables, animal models can provide only limited information regarding the biological interaction with the device. Nevertheless, the models do have value and ViaCyte has conducted extensive animal studies in a variety of species to evaluate PEC-EnCap and Encaptra device formats. The non-clinical data have been helpful but don't compare to the understanding we have gained over the past two years of clinical testing, and will continue to gain from the ongoing clinical evaluation of PEC-EnCap and the Encaptra configurations being tested in this trial.

Thus the primary focus of the ongoing PEC-EnCap (also known as STEP ONE) clinical trial, in addition to demonstrating safety and tolerability, is to understand factors affecting implanted cell survival, related but not limited to the nature and intensity of host response, surgical implantation procedures, anatomical location, and perioperative care. Principal insights into the success of engraftment at this stage of clinical development involve histological analyses of explanted units at various time points (most commonly at 1, 4, and 12 weeks), immune function assessment, periodic ultrasound scans, and a comprehensive battery of clinical assessments and diagnostics.

Importantly, the data and experience to date give us confidence that PEC-EnCap does not present undue risk to patients. Over the course of the trial, product engraftment (i.e., vascularization, cell survival, and differentiation) has steadily improved as variations in methods have been tested and adjunct treatments implemented. Methods yielding increases in cell engraftment at 4 weeks have been observed to translate into prolonged cell survival at 12 weeks in multiple cases, and post-implant differentiation to cells with beta cell markers including insulin, has been observed, an important preliminary indication of feasibility.

In summary, what has been learned thus far includes that the PEC-EnCap product appears to be safe; the Encaptra device appears to be protecting the implanted cells from the patient's adaptive immune system as designed, and in turn the adaptive immune system is not being activated by the product. Critically, 12-week explants from multiple patients have provided an important indication of feasibility for the program, demonstrating substantial cell survival, engraftment, and differentiation to insulin-producing beta cells, including in the larger PEC-EnCap-250 units. By way of reminder, this stage of the trial is being performed with a sub-therapeutic dose so evidence of systemic efficacy is not expected.

Comments on the Review Process:
With regards to the Grants Working Group (GWG) voting on the CLIN2-08839 application, it is our understanding that the GWG vote was at first a tie, with five members voting for a score of "1", five voting for a score of "2", and a single person voting for a score of "3". In other words,

although some favored obtaining some additional information, the overwhelming majority (ten of eleven members) felt that the trial is worth pursuing. We further understand that, to resolve the situation, the GWG made a motion to assign the application a score of "1" which was seconded and passed with a majority of members agreeing to recommend funding of the proposal.

We also understand that, given that ambiguities can arise with the present grant scoring system, CIRM and the ICOC are in the process of reviewing and potentially changing the system. That seems sensible; yet in this context we speculate that CIRM's staff decision to not support the GWG recommendation may at least in part be attributed to the present situation wherein the process is currently in flux, and not a reflection of the merit of the proposed clinical trial per se.

Regardless, the recommendation from the blue-ribbon panel of external scientific reviewers is to fund the application. We believe the millions of patients with type 1 diabetes, including the tens of thousands of afflicted Californians, would likely concur, and hope that the ICOC will support the GWG's final recommendation as well. ViaCyte and the CIRM Diabetes Disease Team have made a tremendous amount of progress in developing this novel product candidate over many years, using CIRM funding judiciously and efficiently along the way. We hope that the ICOC sees the value of this progress, and continues to trust that this team will continue to effectively deliver on the mission of CIRM.

In the interest of clarity, below we will take this opportunity to address the key issues raised by reviewers.

ViaCyte Response to Technical Issues:
The ViaCyte team respectfully thanks the GWG's consideration and thoughtful comments regarding the application. ViaCyte researchers would like to respond to issues raised by the GWG members to provide clarification of the company's rationale and justification for proceeding with this clinical study.

With a significant amount of data from the STEP ONE clinical trial experience to date, including histological assessment of healing and immune responses of over one hundred PEC-EnCap units, including empty device implants as PEC-EnCap Comparators, ViaCyte has determined that the FBR to device biomaterials is the primary factor affecting the healing response, and therefore the cell engraftment process. This is not unexpected.

We believe that refinement of the device materials and configuration may produce significant improvements in the engraftment potential of PEC-EnCap. Further, review of host tissue responses to Encaptra devices and materials implanted into small and large animals has demonstrated that none of the available models adequately reflect the perioperative surgical environment of human patients, nor the complex responses to biomaterials that must be better understood in order to achieve better engraftment of PEC-EnCap implants.

GWG Comment: Additional preclinical testing should be performed prior to implantation of alternate Encaptra configurations in patients.
The biomaterials utilized in the construction of Encaptra and revised configurations have been assessed via biocompatibility testing specified in ISO 10993 and the FDA's Blue Book Memorandum G95-1. These materials have passed all biocompatibility tests, and resulted in very modest host tissue responses in multiple animal models. In contrast, histopathological analyses of PEC-EnCap units explanted from patients, including Comparator Sentinel units containing no PEC-01 cells (empty devices) have identified an inflammatory response related to the device materials that (while likely inconsequential for the vast majority of implantable

medical device applications) may be problematic for long-term survival of cells within the device. The preclinical models designed to demonstrate biocompatibility of materials are not designed to assess encapsulated cell engraftment. ViaCyte has performed Encaptra device testing in swine, the animal model widely regarded as the best analog for human subcutaneous implantation sites. While the subcutaneous structures of swine are similar to those of humans, significant differences in anatomy and tissue response exist such that the pig is not predictive of a human response, and in our pig studies we observed a highly aggressive fibrotic response that is not seen in the patients in the STEP ONE trial. The proposed VC01-102 clinical study in this application, informed by the preclinical experimentation to date combined with the experience and safety track record of the ongoing STEP ONE trial, is designed to maximize the learning in the most relevant "model", the human subject. While one reviewer comment expressed concern that the trial might include too few subjects, in fact up to 10 devices will be implanted in each, so even with only 12 subjects we will have 120 observations, which should be sufficient to draw meaningful conclusions. Moreover, some of the device configurations contain similar or common elements, further aiding the ability to observe correlations between designs and results. We and expert external advisors believe that this is the most effective, accurate, and efficient path forward for achieving success with the PEC-EnCap product.

GWG Comment: The foreign body response to empty Encaptra device configurations should be assessed in comparison to devices containing PEC-01 cells

ViaCyte agrees that comparing empty and cell-containing devices in a clinical context provides important data. In fact, the STEP ONE clinical trial has already incorporated implantation of Comparator Sentinels which are PEC-EnCap-20 implants formulated without PEC-01 cells (empty devices), and without xeno-based excipients. Clinical subjects received both cell-containing PEC-EnCap-20 and Comparator Sentinel units, which were later explanted at the same time points, and from analogous anatomic sites. Histological assessment demonstrated that empty devices produced host tissue responses that were essentially indistinguishable from those of PEC-01 cell-containing PEC-EnCap-20 units, indicating that most or all of this response was related directly to the surgical implantation procedure and Encaptra macroencapsulation device itself, and not to the PEC-01 cells. These data were summarized in the CLIN2-08839 application, page 12 and Figure 2.

STEP ONE study surgeon investigators have spent considerable effort optimizing the implant procedure to minimize tissue trauma, fix the implant within a snug pocket, and avoid the use of tools and techniques that may impair healing. This work has resulted in a procedure that represents the state-of-the-art in subcutaneous surgical placement of Encaptra devices. Thus, we believe that the proposed study with implantation of empty Encaptra devices in human subjects is an effective means to assess host tissue responses to new device configurations. The results are expected to predict the engraftment potential of a PEC-EnCap product that incorporates various Encaptra device improvements.

GWG comment: Additional preclinical work should be performed to demonstrate the benefit of the chosen device iterations.

ViaCyte has performed multiple preclinical studies in SCID-Bg mice that demonstrate significant improvement in PEC-EnCap efficacy as a result of the improved engraftment achieved with the new Encaptra device configurations. Improvements of glucose-stimulated insulin secretion exceeding 50%, relative to the original Encaptra device design have convinced ViaCyte researchers that significant gains in engraftment can be enabled through the introduction of a material layer designed to encourage host tissue ingrowth and vascularization. These data were described on page 15, Figure 4, in the CLIN2-08839 application. The increased insulin secretion observed via a glucose challenge test indicates that both an increased number of beta

cells, and higher level of graft vascularization, result from the device improvements; and these findings were confirmed by histological assessment of the grafts. However, as described above, the FBR to the device in animals has been of limited value; to fully assess the benefits of the changes made, the response needs to be evaluated in humans.

GWG Comment: The immune response related to alternate Encaptra device configurations should be assessed clinically.

In patients implanted with PEC-EnCap units containing PEC-01 cells, multiple immune system parameters were monitored before and after implant, to assess immune sensitization and activation. No evidence of any elevated systemic immune activity was identified. The Encaptra configuration seeks to improve the local host tissue response to the implant in the absence of PEC-01 cells. Any immune-related effect of an empty Encaptra device would be local to the implant site, and restricted to elements of the innate immune system. As such, immune monitoring, which is designed to assess adaptive immunity at a systemic level, would not be expected to provide meaningful data for this study.

In summary, ViaCyte and its collaborators have been making excellent progress in research and product development, with a project entirely consistent with the mission of CIRM, and are now running one of the leading clinical programs in regenerative medicine in California. In the time that CIRM has supported the project, from approximately 2008 to the present, PEC-EnCap has been transformed from a research-level concept to a bona fide product candidate yielding unprecedented new information in clinical investigation. We appreciate that ten of eleven members of the Grants Working Group that initially voted on the CLIN2 application recognize the merit of the application (giving the application a score of “1” or “2”) and that on a re-vote, the majority favored immediate funding. We are gratified with the confidence that the GWG experts have in our team and we will continue to persevere and be successful in this work. Over the course of this program our team has hit and overcome many obstacles, and I believe we have proven time and again that we are leaders in this field, and will use all of the resources available to resolve issues that arise. Lastly, we hope that the enclosed comments have clarified some of the concerns raised by the reviewers.

ViaCyte very much appreciates all of the support that CIRM and the ICOC have provided for the diabetes program. This support has been critical for PEC-EnCap product development, which provides great hope for those suffering with diabetes and their families, and has advanced the forefront of regenerative medicine significantly. We sincerely hope that you will consider voting to fund the CLIN2-08839 application, as it is the next important step in the research required to create a groundbreaking new cell therapy for diabetes.

Sincerely yours,

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