VC01-101

A Prospective, Multicenter, Open-Label, First-in-Human Phase 1/2 Study with Two Cohorts to Evaluate the Safety, Tolerability, and Efficacy of Various Doses of VC-01™ Combination Product in Subjects with Type 1 Diabetes Mellitus

Study Protocol

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ViaCyte Inc.

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A PROSPECTIVE, MULTICENTER, OPEN-LABEL, FIRST-IN-HUMAN PHASE 1/2 STUDY WITH TWO COHORTS TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF VARIOUS DOSES OF VC-01™ COMBINATION PRODUCT IN SUBJECTS WITH TYPE 1 DIABETES MELLITUS

Protocol Number	VC01-101
Compound	PEC-01™ cells with Encaptra® drug delivery system [together known as VC-01™ combination product]
US IND #	016048
Study Phase	1/2
Sponsor Name and Address	ViaCyte Inc., 3550 General Atomics Ct., San Diego, CA 92121
Version Number	2.4 (Site-Specific Amendment)

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PROTOCOL SUMMARY

Title:	*A Prospective, Multicenter, Open-Label, First-in-Human Phase 1/2 Study with Two Cohorts to Evaluate the Safety, Tolerability, and Efficacy of Various Doses of VC-01™ Combination Product in Subjects with Type 1 Diabetes Mellitus*
Description of Agent or Intervention:	*ViaCyte has developed the VC-01 combination product, which is intended to control blood glucose in a more physiologic, sensitive, and homeostatic manner than the various forms of injectable insulin and pump therapies currently available. VC-01 combination product is comprised of two distinct components: (1) PEC-01 pancreatic endoderm cells derived from human embryonic stem cells (hESC) and (2) a durable, cell-impermeable, removable, macroencapsulation device known as the Encaptra drug delivery system.* *During the first three to six months, the VC-01 units are expected to vascularize adequately, and pancreatic progenitor cells are expected to differentiate into mature glucose-responsive, insulin-producing cells, capable of secreting insulin in response to serum glucose concentration.* *Subjects may be implanted with VC-01-250 combination product for dose finding, and smaller VC-01-20 combination product or Comparator sentinels as sentinel units; these are smaller units that will be explanted at various time points and examined ex vivo.*
Study Design:	*This will be an open-label, long-term, first-in-human (FIH) clinical trial in subjects with type 1 diabetes mellitus (T1DM).* *The trial may also evaluate the histological quality of VC-01 in a sample of subjects with type 2 diabetes mellitus (T2DM).*
Study Objectives:	*<u>Objectives</u>: This trial will test whether the VC-01 combination product can be implanted in anatomical locations involving the trunk or extremities and maintained safely for up to two years. There are two distinct cohorts in this FIH trial and each addresses distinct objectives.* *Cohort 1 Study Objective:* • *Assess the local and systemic safety and tolerability of the*

VC-01 combination product when implanted into otherwise healthy subjects with type 1 diabetes mellitus (T1DM) for up to Month 24.

Cohort 2 Study Objectives:

- *Evaluate the clinical efficacy and further assess safety and tolerability of the VC-01 combination product from implantation to Month 24.*
- *Explore effects of weight, gender, BMI, or other potentially interacting factors on the responsiveness of the subjects to the experimental intervention.*

Cohort 1 and 2 Study Objectives (Exploratory):

- *Optimize the recommended surgical implantation procedure, anatomical location, and perioperative care for VC-01.*
- *Assess the effects of the host immune response to implanted VC-01 units.*

Study Endpoints:

The study endpoints vary between the two (2) Cohorts and include safety, tolerability, and efficacy.

- *Safety endpoints include adverse events (AE), the evaluation of the subject's immune response via serum immunoglobulin and hematological assays, and ultrasound imaging of the implanted products.*
- *Tolerability endpoints include the AEs occurring around the time of implantation and beyond.*
- *Efficacy endpoints include the ability of the VC-01 combination product to produce insulin, assessed by stimulated serum C-peptide measurements, changes in usage of exogenous insulin, and measures of glycemic control.*

<u>Endpoints:</u> The primary endpoint of safety will be measured by the AE profile. The primary and secondary endpoints are noted below:

Primary:

- *Cohort 1: Adverse event profile: AE reports, possible*

immune responses (i.e., from the serum immunoglobulin or hematological assays), and implantation site assessments (e.g., fever, erythema, pain, tenderness, induration) for up to four hours post-implantation and at subsequent visits.

- *Cohort 2: Change from baseline in C-peptide $AUC_{0\text{-}4h}$ following a Mixed Meal Tolerance Test (MMTT) at Week 26*

Secondary:

Safety and Tolerability of the VC-01-250 combination product over two years as measured by vital signs, physical exams, concomitant medications, clinical lab tests, quality of life, diabetes treatment satisfaction and number of subjects requiring a premature VC-01 combination product explant due to safety issues, local tolerability, or malfunctions.

Efficacy:

- *Change from baseline in C-peptide $AUC_{0\text{-}2h}$ or $AUC_{0\text{-}4h}$ following an MMTT at Weeks 8, 12, 16, 20, 26 (for $AUC_{0\text{-}2h}$), 39, 52, 78, and 104;*
- *Change from baseline in average daily insulin dose in the seven days preceding Clinic Visits at Weeks 26, 52, 78, and 104;*
- *Change from baseline in frequency of hypoglycemic events at Weeks 26, 52, 78, 104;*
- *Time to onset of biological response of C-peptide following MMTT;*
- *Percent of subjects who achieve exogenous insulin independence;*
- *Percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose at Weeks 12, 20, 26, 39, 52, 78, and 104;*
- *Change from baseline to Weeks 26, 52, 78, and 104 in Patient-Reported Outcome Measure (PROM) scores;*
- *Percent of time spent with blood glucose values at various cut points (e.g., ≤70 mg/dL, ≥180 mg/dL) as measured by each subject's continuous glucose monitoring (CGM) device.*

Cohort 2: Implantation site assessments (e.g., fever, erythema, pain, tenderness, induration) for up to four (4) hours post-implantation and at subsequent visits; and

	incidence of all AEs reported during the study which includes any suspected related immunologic reactions. *Exploratory (both Cohort 1 and 2):* • *Histological results of explanted units and any associated tissue capsule to evaluate cell viability, vascularization, immune response, and/or cell maturation and differentiation.*
Population:	*A total target of up to approximately 69 otherwise healthy subjects will be enrolled into this first-in-human (FIH) clinical trial.* *Cohort 1 will have at least three (3) and up to approximately thirty (30) insulin-requiring diabetic subjects enrolled. Most of these subjects will be T1DM; however up to five (5) subjects with T2DM may be enrolled as part of Cohort 1 if the Sponsor considers it relevant to understanding the engraftment process in the absence of autoantibodies present in T1DM. A total of 30 subjects may be enrolled in Cohort 1.* *Cohort 2 will have approximately 36 to 39 T1DM subjects enrolled. This gives a total study size of up to 69 subjects.* *Note that the data from the T2DM subjects will be collected and summarized separately from that for the T1DM subjects.*
Phase:	*1/2*
Number of Sites:	*Approximately four to six*
Study Duration:	*Screening period is approximately four (4) weeks. Enrolled subjects with T1DM are expected to have the VC-01 product implanted for two years; after all VC-01 units have been explanted, each subject will be required to be followed in a 3-year long-term follow-up study (VC01-201).* *Subjects with T2DM are expected to have the VC-01 product implanted for up to approximately six months.*
VC01-101 Subject Participation Duration:	*Two (2) years for T1DM subjects.* *Up to seven (7) months for T2DM subjects.*
Estimated Time to	*One to two years recruitment estimated (combined for both*

Complete Enrollment: *cohorts)*

LIST OF ABBREVIATIONS

ADDQoL	Audit of Diabetes-Dependent Quality of Life
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CHF	Congestive Heart Failure
GMP	Certified Good Manufacturing Procedures
CRF	Case Report Form (electronic or paper)
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
DTSQ	Diabetes Treatment Satisfaction Questionnaire in status (DTSQs) and change (DTSQc) version
ECG	Electrocardiogram
EIU	Exposure in Utero
EoP2	End of Phase 2
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First-in-Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
hESC	Human Embryonic Stem Cell(s)
HIPAA	Health Insurance Portability and Accountability Act
HU	Hypoglycemia Unawareness
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEQ	Islet Equivalents
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
JDRF	Juvenile Diabetes Research Foundation
KM	Kaplan-Meier
LSLV	Last Subject Last Visit
LSM	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed Meal Tolerance Test

N/n	Number (typically refers to subjects)
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
PE	Physical Examination
PEC	Pancreatic Endoderm Cells
PEC-01	PEC-01 Cells (drug product)
PI	Principal Investigator
PROM	Patient Reported Outcome Measures
PT	Preferred Term
QC	Quality Control
REB	Research Ethics Board (Canada)
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SE	Standard Error
SHE	Severe Hypoglycemic Event(s)
SMBG	Self Monitoring of Blood Glucose (i.e., fingerstick)
SOC	System Organ Class
SOP	Standard Operating Procedure
SSA	Site-Specific Amendment
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
US	United States
VC-01	VC-01 Combination Product

1. INTRODUCTION

1.1. Background Information and Scientific Rationale

Diabetes mellitus, a life-threatening disease growing at an alarming rate, has more than doubled in prevalence over the last thirty years. [REF 1] In 2012, the number of people worldwide with diabetes was estimated to be between 347 and 371 million (approximately 5% of the world's population). According to the 2011 National Diabetes Fact Sheet from the Centers for Disease Control (CDC), there are 25.8 million people of all ages living with diabetes in the United States: 18.8 million of those being diagnosed and 7 million undiagnosed [REF 2]. Of the people diagnosed with diabetes, approximately 5%, or 1 million, have type 1 diabetes mellitus (T1DM) and require exogenous insulin injections every day to survive [REF 2].

The hallmark of diabetes is elevated blood glucose levels. Over time, this chronic hyperglycemia frequently results in both microvascular (retinopathy, neuropathy, nephropathy) and macrovascular (atherosclerosis, cardiac disease) complications, which severely increase morbidity and mortality, and diminish the patient's quality of life. Treatment costs of diabetes and its complications range from $174 billion to $240 billion dollars annually in the US alone, and care for people with diagnosed diabetes accounts for greater than one in five health care dollars. [REF 2, 3] Medical care costs for people with diabetes are more than two times higher than for those without diabetes [REF 2].

Diabetes patients who require insulin treatment include all patients with T1DM, which is caused by loss of insulin-producing pancreatic beta cell mass, and 20-30% of patients with type 2 diabetes mellitus (T2DM), who require insulin as adjunctive therapy. Each year, more than 15,000 children and 15,000 adults (approximately 80 people per day) are diagnosed with T1DM in the US alone [REF 2].

There is no known way to prevent or cure T1DM [REF 2]. Treatment involves frequent, painful, and cumbersome blood glucose monitoring followed by insulin injection. This standard of care can be woefully inadequate. Subjects employing frequent "fingerstick" blood glucose monitoring are able to maintain strict glycemic control within the ADA-specified optimal range less than 30% of the time. [REF 4] The most intensive forms of insulin therapy involve the use of Continuous Glucose Monitoring (CGM) systems, self-monitoring (fingerstick) blood glucose measurement with portable meters, and implanted insulin pumps. Yet even these technologically advanced systems require significant patient management and cannot control glycemia perfectly. Patients using CGM may still be hyperglycemic almost 30% of each day. [REF 4]

Importantly, insulin therapy also leads to periods of hypoglycemia. Patients using CGM may be hypoglycemic approximately 8% of each day, with a propensity for hypoglycemic events to occur at night. [REF 4] In some cases, severe hypoglycemic events (SHE), i.e., those requiring the aid of another person to administer carbohydrates, glucagon, or other resuscitative assistance, can lead to seizures, unconsciousness, coma, and death. Importantly, a history of hypoglycemia can predispose patients to episodes of hypoglycemia unawareness (HU), which increases their risk of severe hypoglycemia and serious sequelae by at least 6-fold. [REF 5] Hypoglycemia, like hyperglycemia, should be avoided if possible.

Many new approaches to treatment of T1DM are being pursued including immunologic intervention in disease mechanisms, beta-cell regenerative and/or replacement therapies, and engineering solutions to enhanced glucose monitoring and insulin delivery. One such treatment being developed is the pancreatic islet transplant which may employ cells of either porcine or human origin. Although allogeneic islet cell transplantation has achieved insulin independence in some patients, the success rate from center to center has varied widely, and the duration of effect has been limited. Furthermore, islet transplant has two significant disadvantages. First, pancreatic islet transplantation requires chronic immunosuppression for the lifetime of the graft, which adds substantial risk including severe infection and potential progression of occult cancers. Second, its availability is limited by an insufficient supply of acceptable human pancreata as source material.

1.2. Investigational Product

ViaCyte has developed the VC-01 combination product which is intended to control blood glucose in a more physiologic, sensitive, and homeostatic manner than the various forms of injectable insulin currently available. The VC-01 combination product is comprised of two distinct components: PEC-01 pancreatic endoderm cells derived from human embryonic stem cells (hESC), and a durable, cell-impermeable, removable, macroencapsulation device (known as the Encaptra® drug delivery system). The VC-01 combination product may be implanted in an outpatient procedure.

The VC-01 combination product may be considered a pro-drug inasmuch as the pancreatic progenitor cell component matures to glucose-responsive, insulin-secreting cells only after implantation and further differentiation. The insulin-producing capability of VC-01 increases gradually; in nonclinical studies, the product reaches glucose-responsive activity capable of regulating host glycemia at two to three months after implantation. Subcutaneously in rodents, the cells in the device differentiate into pancreatic endocrine cells, including those that express insulin and release it in a glucose-responsive fashion as well as cells expressing glucagon, somatostatin, pancreatic polypeptide, and ghrelin, similar to human islet tissue. Importantly, host vascularization accompanies graft maturation to provide a source for oxygen and other nutrients, and a mechanism to deliver insulin and other graft-expressed hormones to the body.

Glucose-responsive secretion of insulin by a therapeutic dose of the VC-01 combination product would be expected to maintain better glycemic control than the current standard of care. If found to be safe and effective, VC-01 may prevent both the acute dangers of hypoglycemic excursion (e.g., SHE) and the more chronic complications of diabetes (e.g., microvascular and macrovascular disease). Moreover, VC-01 may alleviate the frequent blood glucose checks and insulin injections required each day. Thus, it is anticipated that VC-01 might significantly improve quality of life and treatment satisfaction as compared to currently available therapies.

PEC-01 is manufactured to satisfy rigorous quality and safety requirements. The manufacturing process was designed to eliminate pluripotent stem cells and produce a highly enriched pancreatic endoderm population. No potentially dangerous cell type has been identified in over 1,000 VC-01 units implanted in nonclinical animal studies or during the early, limited, clinical use of the product in this FIH trial.

A unique and important feature of VC-01 is the encapsulation of PEC-01 in the Encaptra drug delivery system, which affords numerous benefits noted below.

- The Encaptra drug delivery system is macroporous, permitting free passage of oxygen, nutrients, proteins, and other macromolecules required to maintain the implanted cell viability and function.
- The Encaptra drug delivery system is impermeable to implanted and host cells. Thus, it permanently contains PEC-01 at a defined location, preventing them from distributing into host tissue.
- Once implanted, VC-01 can be monitored via ultrasound for evidence of device lumen expansion as an indicator of potentially unsafe, off-target cell growth.
- The Encaptra drug delivery system also prevents direct contact between the immune cells of the host and the cells of the graft. This physical barrier interferes with antigen presentation and disrupts the cell-mediated effector functions of the typical immune response. Similar physical barrier membrane systems have been shown to protect cells from allo- and auto-immune rejection [REF 7] as well as to protect against sensitization of the host. [REF 6] In this way, immune-protection afforded by the device eliminates the need for, and the attendant safety risks of, chronic immunosuppression.
- Finally, in the event of loss of function, adverse reaction, or other potential safety concern, VC-01 units can be promptly removed in an out-patient procedure. The ability to explant the entire graft (and all cells contained in the graft) offers a unique safety advantage as compared to other cell therapies in which implanted cells cannot be retrieved.

1.3. Nonclinical Information

1.3.1. Evaluation of Safety of PEC-01 Cells

Nonclinical evaluation of the safety of PEC-01 includes characterization of the source hESC starting material, intermediate cell populations during PEC-01 drug substance manufacture, and the resulting differentiated pancreatic endoderm cell population. Evaluations of the hESC Master Cell Bank and Working Cell Bank were completed in accordance with applicable guidance documents. For PEC-01 cellular manufacture, raw materials have been subjected to a risk assessment and will meet acceptance criteria for Phase 1 clinical manufacturing. To ensure sufficient safety of PEC-01, GMP manufacturing of PEC-01 will be performed in compliance with regulations and quality control procedures appropriate for the phase of clinical use. Characterizations of PEC-01 include assessment of identity, purity, quality, and stability.

1.3.2. Nonclinical Evaluation of Safety of the Encaptra Drug Delivery System Component

Nonclinical evaluations of the Encaptra drug delivery system include device biocompatibility studies and device integrity studies. Additional testing performed to date has demonstrated that the Encaptra device is capable of supporting survival, differentiation, and maturation of PEC-01

in vivo. Feasibility of utilizing the device to prevent biodistribution of implanted cells and to provide allogeneic immune protection against host cells has been demonstrated. Design verification activities are focused on confirming that the device membrane maintains its ability to block cell migration through the product life cycle, on assessing material stability, and on implementing complementary manufacturing quality controls to ensure that all devices produced will provide adequate safety performance. Completed studies, conducted in accordance with GLP, confirm that the device passes all biocompatibility tests. The Encaptra device is expected to significantly contribute to the safety profile of the VC-01 product by providing biocompatible and biostable encapsulation that prevents implanted cells from directly contacting host tissue.

1.3.3. Nonclinical Evaluation of Safety and Efficacy of VC-01

Nonclinical evaluations of VC-01 safety and efficacy include [redacted] studies conducted in accordance with Good Laboratory Practices (GLP). A total of [redacted] were implanted with VC-01 in these [redacted] GLP studies. Safety assessments in these studies included: necropsy with organ weights, full organ panel histopathology, histopathology on the implant and surrounding tissue, and clinical pathology including blood chemistry, hematology, coagulation analysis, and urinalysis. The completed studies demonstrated excellent tolerability of the graft with an absence of any related toxicity on any of these measures, as well as an absence of tumor formation. Each [redacted] in these studies was implanted with a cell dose [redacted], on a per kg basis, than the initial dose planned for evaluation in the first-in-human clinical trial (VC01-101), and thus these GLP studies represent a robust nonclinical demonstration of VC-01 combination product safety.

Five (5) different lots of PEC-01 were used in these three GLP studies with no evidence of teratoma formation. However, when Encaptra devices were loaded with PEC-01 "spiked" with small proportions of undifferentiated hESC, or loaded with pure undifferentiated hESC (as a positive control) and implanted into [redacted], teratomas were observed (internal study [redacted]). These intentionally generated teratomas were contained by the device. While hESC have not been observed in the PEC-01 cell population, all lots of cell product used to manufacture VC-01 for this clinical trial will be QC tested for hESC contamination prior to product release, nevertheless, as a safety precaution. If a teratoma were to grow in a device, it would be detected via non-invasive imaging (see Section 7.6).

Studies conducted under GLP also characterize glucose-responsive human C-peptide secretion and the capacity of VC-01 to appropriately regulate host glycemia. Moreover, each graft is examined histologically, including a determination as to whether there are host (mouse) cells inside the device. As host cells always enter a device if they are able, i.e., if there is a breach in the device, the absence of host cells within the device demonstrates the integrity, specifically the cell impermeability, of the encapsulating device.

Classical biodistribution studies and pharmacokinetic studies, namely absorption, distribution, metabolism, and excretion, are not particularly applicable to the VC-01 product or its cellular and encapsulating device components. Instead, pharmacodynamic studies with the VC-01 product include a "meta-analysis" of over [redacted] implanted with the VC-01-20 product. These studies demonstrate:

- Consistent kinetics for acquisition of glucose-responsive C-peptide secretion,

- C-peptide secretion reaching levels capable of regulating glycemia in the absence of endogenous host beta cells,
- No induction of hypoglycemia, and
- Maintenance of durable therapeutic properties throughout the duration of implantation (commonly six to nine months).

Also, with VC-01 implanted, [redacted] non-fasting blood glucose levels are lowered to levels more typical of non-fasting human blood glucose, and once achieved, stable blood glucose levels are subsequently observed throughout duration of the VC-01 product implant. Finally, because the VC-01 product is designed to deliver PEC-01 within the Encaptra device, the product is readily retrievable via an explantation procedure, allowing for immediate cessation of drug delivery if indicated.

Nonclinical efficacy dose-range finding studies have been conducted. A principal conclusion from these studies is that the ultimate therapeutic capacity of the VC-01 combination product is not particularly dependent upon the number of cells administered; instead it is dictated by the capacity/volume of the encapsulation device. For example, units of a given size (e.g., VC-01-20) ultimately achieve [redacted] loaded inside prior to implantation. This is likely because the cells can proliferate to fill the device to capacity, and therefore can compensate for "under-loading" the device. Thus, it is expected that the dose delivered is established more so by the number and size (capacity) of units implanted than the absolute number of cells delivered upon implant.

1.4. Potential Clinical Risks and Benefits

There has been limited clinical experience with this product such that no definitive risks or benefits can be concluded yet.

In order to participate in this clinical trial, subjects will not be asked to stop their exogenous insulin therapy. Therefore, subjects are not expected to undergo periods of ineffective diabetes therapy during study participation. If the investigational product demonstrates efficacy, however, the dosing requirement for exogenous insulin may decrease over time.

1.4.1. Potential Risks

As there has been limited clinical experience with this product, the potential risks for study participation are hypothetical at this stage. Potential risks are noted below.

- There are inherent surgical risks during the implantation and explantation (removal) of the VC-01 units including pain, bleeding, hematoma, seroma, tenderness, redness, and infection. With any implant procedure, the possibility of migration or extrusion of the implant exists, along with the need for explantation. Steps will be taken to minimize the risks and to make the subject comfortable during the procedure with anesthetic and post-procedure analgesia.
- The use of anesthesia itself may cause side effects. The type(s) of anesthesia used during the implantation and explantation procedures will be determined by the investigator or surgeon. Side effects may include, but are not limited to:

  - Local anesthesia: Stinging and burning for a few seconds before numbing the skin and tissues. Other less likely side effects include nausea, vomiting, dizziness, drowsiness, local allergic reactions (e.g., redness, itching, and rash), low blood pressure, weakness, severe numbness or tingling, ringing in ears, blurry or double vision, slurred speech, metallic taste in mouth, mental status change, muscle twitching, and seizures.
  - General anesthesia: Harm to the vocal chords, heart attack, lung infection, stroke, trauma to the teeth or tongue, or temporary mental confusion. Rarely, waking during anesthesia or death may occur.
  - Conscious sedation: Difficulty breathing.

- After implantation and vascularization of the implanted units, there may be an increased risk for hypoglycemic events. Although the risk for hypoglycemia from the grafted units is minimal based upon preclinical results, as the implanted cells begin producing insulin, subjects and investigators will need to monitor fingerstick blood sugars closely to appropriately decrease the amount of required exogenous insulin.
- There is a risk that the implanted product will have a shorter than expected duration of efficacy or does not work as expected. [redacted] Cell viability and product function of the VC-01 unit exceeds the lifetime of animal models. The duration of exposure proposed for this clinical trial is two years. There are safety-related, strictly-defined stopping and explant rules noted in Section 8.6.
- There are risks that the implanted product may limit the subject's ability to be a candidate for future islet cell transplantation.
- There is a potential hypothetical risk of off-target cell growth (e.g., teratomas). Ultrasound monitoring of the implanted units will occur throughout the trial.
- There is a potential risk of immune reactions and inflammatory responses due to the implantation of the graft. Steps have already been taken in the design of the device to minimize/eliminate this risk, but as the grafts have not yet been studied in a human population, there remains a potential risk.
- There is a potential that the implanted units may rupture or break. [redacted] However, the device will not prevent penetration by a sharp object (e.g., insulin needle). If the device membrane were to be breached, the most likely effect would be a loss of efficacy.
- As human cells are being implanted, there is also a small risk that the subject could contract a disease or condition transmitted through the allogeneic cell line.

1.4.2. Known Potential Benefits

As VC-01 has not been studied clinically beyond the early stages of this trial, there are no known benefits. However, there may be several potential benefits of this therapy noted below.

- Improved glycemic control
- Reduction in exogenous insulin dose
- Reduction in the number of insulin injections and/or complete elimination of exogenous insulin injections
- Reduction in frequency of blood glucose monitoring
- Reduction in the number of hypoglycemic events
- Reduction in the risk of micro- and macro-vascular complications
- Improvement in Quality of Life from an economic standpoint (e.g., decreased exogenous insulin requirements, fewer self-monitoring blood glucose supplies)
- Improvement in Quality of Life from a lifestyle standpoint (e.g., dietary freedom)
- Improvement in Diabetes Treatment Satisfaction

The planned number of VC-01 combination products implanted in Cohort 2 is higher than the planned number of units implanted in Cohort 1. While subjects enrolled in Cohort 2 will have a higher likelihood of experiencing clinical benefit, it is possible that subjects in Cohort 1 may experience some degree of clinical benefit as well.

2. OBJECTIVES AND ENDPOINTS

This first clinical trial will test whether VC-01 can be implanted and maintained safely for at least two years in T1DM subjects. During the first three to six months, the Encaptra device is expected to vascularize adequately, and pancreatic progenitor cells are expected to differentiate into mature glucose-responsive, insulin-producing cells, capable of secreting insulin in response to serum glucose levels. This device is anticipated to block direct antigen presentation and disrupt cell-mediated effector functions of both the auto- and allo-immune response.

The safety endpoints will be measured by the AE profile. In addition, potential decreases in the number of hypoglycemic events will be evaluated as this is expected to be one of the first clinical indications that the implanted product is exerting a clinical response. Other endpoints may include the ability of VC-01 to produce insulin, assessed by serum C-peptide measurements, changes in usage of exogenous insulin, and measurements of glycemic control. The subject's immune response will be evaluated via serum immunoglobulin and hematological assays.

On an exploratory basis, the recommended surgical technique, anatomical implant location, and perioperative care associated with VC-01 implantation will be evaluated through histological analysis of explanted units and any associated tissue capsules. Furthermore, a histological evaluation of explanted VC-01 units in T1DM and T2DM patient populations will provide comparative data of the host immune response to the implanted units since the autoantibodies associated with T1DM are not present in the T2DM population.

2.1. Study Objectives

There are two distinct cohorts in this FIH trial and the cohorts serve different objectives.

Cohort 1 Study Objective (for Subjects with T1DM):

- Assess the local and systemic safety and tolerability of VC-01 when implanted into at least three (3), and up to approximately 30, otherwise healthy subjects with type 1 diabetes mellitus (T1DM) enrolled to Month 24. Although up to five (5) T2DM subjects may also be enrolled during the Cohort 1 period (in lieu of the same number of T1DM subjects), all data from the T2DM subjects will be summarized separately from the T1DM subjects enrolled in Cohort 1 (Section 10).

Cohort 2 Study Objective:

- Evaluate the clinical efficacy and further assess safety and tolerability of the VC-01 product when implanted into approximately 36 otherwise healthy subjects with T1DM enrolled in parallel to Month 24. Data from different parameters will be evaluated to understand whether there are effects based on weight, gender, BMI, or other confounding factors.

Cohort 1 and 2 Study Objective (Exploratory):

- Optimize the recommended implantation surgical technique, anatomical location(s), and perioperative care based on the data collected on Cohort 1 and Cohort 2 subjects. Updates to the recommended surgical implantation procedures will occur as needed after consultation between the Sponsor and Investigator and/or Site Surgeon and will be communicated to the sites to support the safety, tolerability, and efficacy profile of VC-01.
- Assess the effects of the host immune response to implanted VC-01 units.

2.2. Study Endpoint Measures

The study endpoints vary between the two cohorts and include safety, tolerability, and efficacy. Additionally, there is an exploratory endpoint related to the surgical implantation procedure and anatomical locations of VC-01, perioperative care, and host immune response, which includes both Cohorts (Section 2.5).

- Safety endpoints include AEs over two years and include the evaluation of the subject's immune response via serum immunoglobulin and hematological assays and ultrasound imaging of the implanted products.
- Tolerability endpoints include AEs occurring around the time of the surgical implantation and beyond.
- Efficacy endpoints include the ability of VC-01 to produce insulin, assessed by serum C-peptide measurements following a Mixed Meal Tolerance Test (MMTT), changes in recorded usage of exogenous insulin and other measures of glycemic control.

As a measure of both safety and efficacy, potential decreases in the number of hypoglycemic events (HE; SHE) will be evaluated as this is expected to be one of the first clinical manifestations of efficacy that may occur at marginal doses.

2.3. Primary Endpoint Measures

Primary Endpoint / Cohort 1:

- Adverse Event profile: Incidence of all AEs reported during the study. This includes any suspected related immunologic reactions.

Primary Endpoint / Cohort 2:

- Change from baseline in C-peptide $AUC_{0\text{-}4h}$ following an MMTT at Week 26.

2.4. Secondary Endpoint Measures

Secondary Safety and Tolerability Endpoints:

- Vital signs.
- Physical examinations.
- Concomitant medications.
- Clinical lab tests.
- Number of subjects requiring a premature explant of the VC-01 product due to safety or tolerability issues or malfunction.
- Implantation site assessments (e.g., fever, erythema, pain, tenderness, induration) for up to four hours post-implantation and at subsequent visits.

Secondary Efficacy Endpoints:

- Change from baseline in C-peptide $AUC_{0\text{-}4h}$ following an MMTT at Weeks 52 and 104; and change from baseline in C-peptide $AUC_{0\text{-}2h}$ following an MMTT at Weeks 8, 12, 16, 20, 26, 39, 52, 78, and 104.
- Change from baseline in average daily exogenous insulin dose in the seven days preceding Clinic Visits at Weeks 26, 52, 78, and 104.
- Change from baseline in frequency of hypoglycemic events at Weeks 26, 52, 78, 104.
- Time to onset of biological response of C-peptide following MMTT.
- Percent of subjects who achieve exogenous insulin independence; percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose at Weeks 12, 20, 26, 39, 52, 78, and 104.
- Change from baseline to Weeks 26, 52, 78, and 104 in Patient-Reported Outcome Measure (PROM) scores.

- Percent of time spent with blood glucose values at various cut points (e.g., ≤ 40 mg/dL, ≤50 mg/dL, ≤60 mg/dL, ≤70 mg/dL, ≥180 mg/dL, ≥250 mg/dL) as measured by each subject's CGM machine.

Secondary Safety and Tolerability Endpoint / Cohort 2:

- Incidence of all AEs reported during the study. This includes any suspected related immunologic reactions.

2.5. Exploratory Endpoint Measures

Exploratory Endpoint / Cohort 1 and 2:

- Histological analysis of explanted units and any associated tissue capsules to evaluate cell viability, vascularization, cell maturation and differentiation, and the host immune response as a means to optimize the surgical implantation procedure, anatomical location, perioperative care and assess the host immune response to implanted units.

3. STUDY DESIGN

In this prospective, open-label, multicenter trial, subjects will have up to two or more primary VC-01-250 units and one or more smaller sentinel units implanted in anatomical locations [redacted] suitable for implantation, as deemed appropriate by the Investigator and/or surgeon after consultation with the Sponsor. Documentation of the implant plan for a subject will be provided to the Investigator by the Sponsor. [redacted]).

There are two distinct cohorts in this trial:

- Cohort 1 (Section 3.1)
- Cohort 2 (Section 3.2)

At the end of the up to 2-year treatment period for the T1DM subjects (up to 6 months for T2DM subjects), all remaining implanted units will be surgically removed and each enrolled subject will be required to participate in a 3-year follow-up (non-intervention) study. The details of this 3-year follow-up safety study are established in protocol VC01-201 and may be amended based on the data collected in this FIH trial; the primary purpose will be to ensure that there are no long-term safety issues.

Each Cohort is described in further detail below.

3.1. Cohort 1

Cohort 1 may enroll up to approximately thirty (30) insulin-requiring diabetic subjects at one or more investigative sites in the US and/or Canada. Most of these subjects will be T1DM; however this may include up to five (5) T2DM subjects. Subjects in Cohort 1 will have up to two of the larger VC-01-250 units implanted, along with four (4) to six (6) of the sentinel units,

which may be the smaller VC-01-20 and/or Comparator sentinel. Up to three (3) of the sentinels implanted in each Cohort 1 subject may be a Comparator sentinel that does not contain PEC-01, to be determined by the Sponsor with notification to the Investigator. The implant of Comparator sentinels may help identify the host response specific to both the device and cellular components of VC-01 (Section 7.9), and implanting up to three (3) Comparator sentinels will permit evaluation of changes to the host response over different post-implant time periods, in direct comparison to VC-01 sentinel units.

Each Cohort 1 subject with T1DM will be followed for two years as outlined in Table 1 – Schedule of Assessments (Cohort 1). Cohort 1 subjects with T2DM will be followed for up to 6 months (26 weeks) as outlined in Table 3. T2DM subjects will be implanted with VC-01 units under the same requirements outlined above, but the duration of treatment will be shortened to a maximum of 26 weeks.

For all subjects enrolled during Cohort 1, if a severe, treatment-related AE is spontaneously reported to have occurred within the first two weeks of a subject's implant, subsequent implantation of subjects in Cohort 1 may be deferred until formal review of the AE is completed. But otherwise, subjects may be concurrently enrolled in Cohort 1.

After a minimum of three (and up to approximately 30) total subjects in Cohort 1 have reached Visit 7 (Week 4), the independent Data Safety Monitoring Board (DSMB) will meet. The cumulative data collected from Cohort 1 in all subjects up until that time will be evaluated. It is the DSMB's decision to trigger the start of Cohort 2. Given the logistical requirements of collecting and cleaning the cumulative data of subjects in Cohort 1, convening a meeting of the DSMB to review and approve the data, and the time required to initiate sites participating in Cohort 2, the interval from the time the last subject in Cohort 1 is implanted (Visit 3/Day 1) until the first subject of Cohort 2 is implanted will be a minimum of 12 weeks. By such time, it is expected that any significant safety signal would present, if one were to exist.

The DSMB will not meet regularly during Cohort 1 unless the Sponsor seeks an independent DSMB review based on Sponsor or Investigational Review Board (IRB) or Research Ethics Board (REB) recommendations for managing AEs. The DSMB chair and/or the entire DSMB may receive regular updates as to the progress of the trial.

3.2. Cohort 2

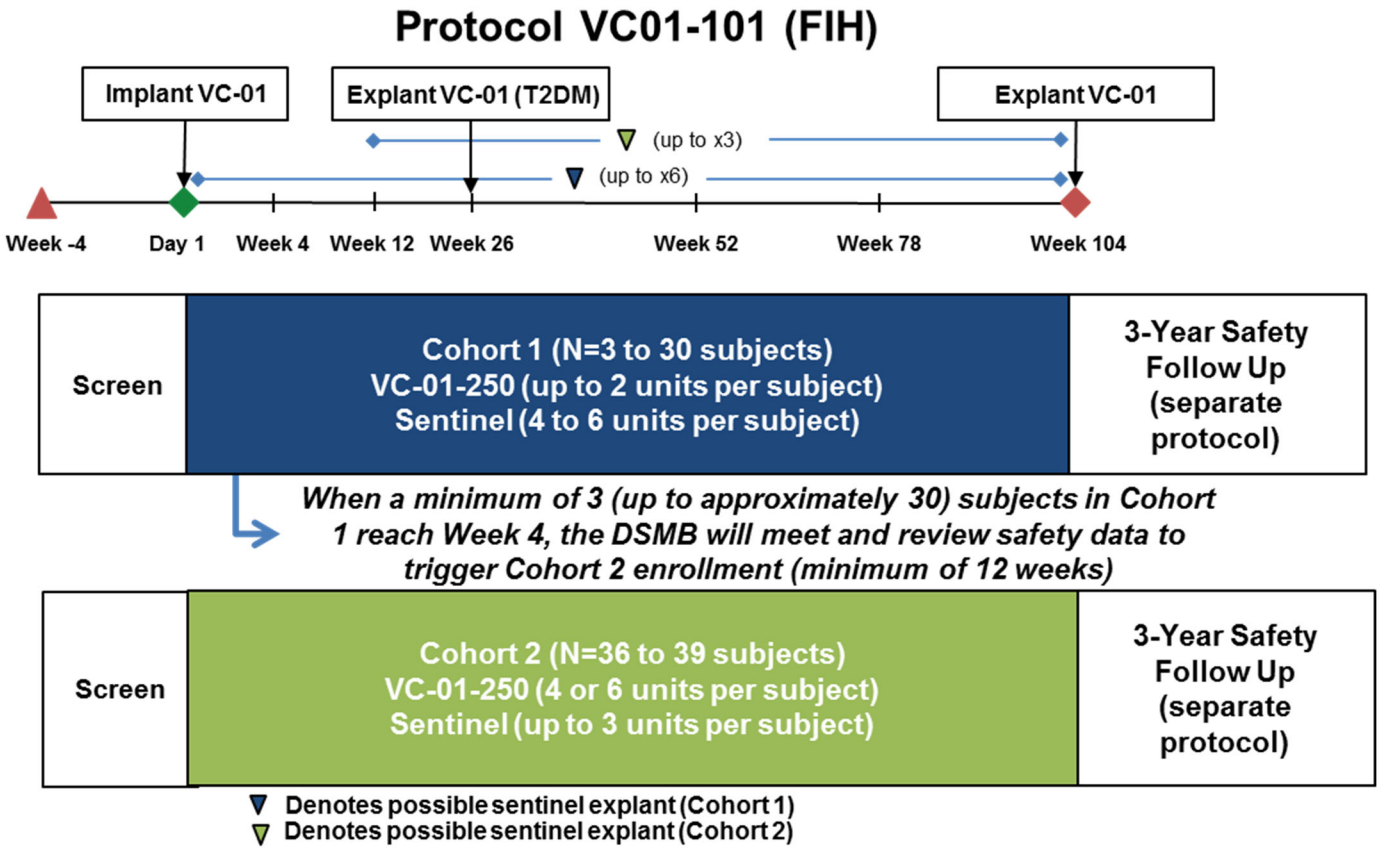
Cohort 2 will include approximately 36 to 39 T1DM subjects enrolled competitively at approximately four to six clinical sites in the US and/or Canada and includes the site(s) enrolling subjects into Cohort 1. Each subject will be followed as outlined in Table 2 – Schedule of Assessments (Cohort 2). The number of VC-01-250 units to be implanted in Cohort 2 subjects will be determined by the maximum C-peptide response (basal or stimulated) observed only in subjects in Cohort 1 with T1DM following an MMTT based on available data at the time Cohort 2 is initiated:

- If the maximum C-peptide [redacted], six (6) VC-01-250 units and up to three (3) VC-01-20 sentinel units will be implanted in the Cohort 2 subjects.
- If the maximum C-peptide [redacted], then four (4) VC-01-250 units and up to three (3) VC-01-20 sentinel units will be implanted.

- Sentinel units will be explanted at time points to be determined by the Sponsor based on information gathered from previously-explanted sentinels. Generally, it is the intention of the Sponsor that subjects enrolled early in Cohort 2 will have some sentinels explanted during the early phase of the treatment period. However, the remaining sentinels and subsequent subjects may have sentinels explanted at visits in the latter phase of the treatment period.

The number of VC-01-250 units and VC-01-20 sentinel units implanted into the Cohort 2 subjects may require adjustment depending on the anatomical locations available for implantation. Individual differences in a subject's anatomical configuration may result in insufficient area available for all of the planned units to be implanted. The ViaCyte clinical team will work with the site Investigator and/or surgeon to confirm the number and location(s) of VC-01-250 units and VC-01-20 sentinel units to be implanted during Cohort 2 prior to each subject's scheduled implantation. At the time of implantation procedure, if the scheduled number of units cannot be feasibly implanted, then this will be communicated to the Sponsor on the day of the surgery and properly documented.

Cohort 2's primary efficacy endpoint will be the change of $AUC_{0\text{-}4h}$ C-peptide after an MMTT at Week 26.



4. STUDY POPULATION

This trial can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Number of Patients and Sites

The subjects in Cohort 1 will be recruited from one or more sites in the United States and/or Canada. A target minimum of three evaluable subjects will be enrolled, but up to approximately 30 total subjects may be enrolled in Cohort 1 if the Sponsor and/or DSMB determine that additional subject data are necessary to properly evaluate the investigational product and/or the implantation procedure. Up to thirty (30) subjects with insulin-requiring diabetes, the majority of which will be T1DM subjects but may include up to five (5) subjects with T2DM, may be enrolled during Cohort 1. Cohort 2 will enroll approximately 36 to 39 subjects from approximately four to six sites in the United States and/or Canada. This includes any site(s) participating in Cohort 1. The total enrollment possible for the trial (Cohort 1 and Cohort 2) is up to 69 subjects.

4.2. Entry Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the Investigator's trial team before subjects are included in the trial. Subjects must meet all of the following inclusion criteria at the time of the Screening Visit 1 (unless otherwise specified) to be eligible for enrollment into the trial. If screening laboratory test result(s) exclude a subject and the investigator is reasonably certain that the results may be due to a lab error or may have been flawed for another reason, the lab test(s) may be repeated once during the screening period without prior permission from the Sponsor or its designee.

4.2.1. Inclusion Criteria

The following inclusion criteria are applicable to all subjects:

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject has been informed of all aspects of the trial.
2. Males and females who are non-pregnant and of non-childbearing potential (see Section 4.5.5.1) ages 18-55.
3. Cohort 1: Diagnosis of type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) for a minimum of 3 years, on a stable (at least 3 months) insulin regimen. Subjects with T2DM may also be on an oral anti-diabetic medication regimen.

   Cohort 2: Diagnosis of type 1 diabetes mellitus (T1DM) only for a minimum of 3 years.
4. Stable, optimized diabetic regimen for at least 3 months. Variations in the dose of insulin are permitted and can still meet the definition of stable insulin dose [refer to the study reference manual for additional guidance on acceptable variations]. Subject should be under the care of a physician using intensive insulin therapy with therapeutic goals

consistent with standard of practice (e.g., American Diabetes Association guidelines) for a minimum of 6 months.

5. The subject is an acceptable candidate for implantation and explantation of VC-01 combination products as determined by the site surgeon and Investigator.
6. Willing and able to comply with scheduled visits, treatment plan, post-surgical care and restrictions, laboratory tests, fingerstick blood glucose monitoring, and other study procedures.
7. Fluent in English.

The following additional inclusion criteria apply only to subjects with T1DM:

8. Insulin dosage at screening of ≤1 unit/kg/day (using previous seven days as average).
9. Willing to use a Continuous Glucose Monitoring (CGM) System as instructed and comply with system requirements during the trial. Note: Use of the standard CGM System provided by the Sponsor is required.
10. Willing and able to comply with daily entries on a study diary. The subject must demonstrate compliance with daily entries on the diary between Visits 2 and 3.

4.2.2. Exclusion Criteria

The following exclusion criteria are applicable to all subjects. Subjects presenting with any of the following will not be included in the trial.

Disease-specific:

1. Medical history of islet cell, kidney, and/or pancreas transplant.
2. Occurrence of two or more severe, unexplained hypoglycemic events (SHE; defined as requiring the assistance of another individual) within six months of Visit 3 (Day 1/Enrollment).
3. Cohort 1: Known causes of diabetes other than T1DM or T2DM.

   Cohort 2: Known causes of diabetes other than T1DM.
4. Diabetic complications such as kidney disease (Stage 3 to 5), hypoglycemic unawareness, renal dysfunction (macroalbuminuria defined as protein of 2+ or greater on dipstick, MDRD eGFR <60 ml/min/1.73m^2), previous diagnosis of proliferative retinopathy by medical history, diabetic foot ulcers, amputations attributable to diabetes, and/or severe peripheral neuropathy.
5. Widely variable patterns of glycemic control in the clinical judgment of the Principal Investigator (PI) [refer to the study reference manual for additional guidance].

Medical History:

6. Significant skin conditions involving the area(s) targeted for implantation. Examples include but are not limited to recurrent boils/furuncles, extensive surgery or scarring, or lipodystrophy.
7. Subjects routinely consuming >two alcoholic drinks per day or >14 alcoholic drinks per week or engages in binge drinking. One alcoholic drink is defined as 5 oz (150 mL) of wine, 12 oz (350 mL) of beer, or 1.5 oz (50 mL) of 80-proof liquor. Binge drinking is defined as a pattern of five or more alcoholic drinks (males) or four or more alcoholic drinks (females) in roughly two hours.
8. Positive urine drug screen for substances of abuse at screening or enrollment visit. Infrequent, recreational use of certain substances may be allowed by the PI after consultation with the Medical Monitor and/or Sponsor.
9. Prior history of malignancy with the exception of:
    a. Basal cell carcinoma of the skin;
    b. Squamous cell carcinoma of the skin that has been recurrence free for ≥five years;
    c. Appropriately treated in situ carcinoma of the cervix.
10. Known allergies to portions of the cellular excipients used as cell preservation solution or the PEC-01 manufacturing process (i.e., bovine, porcine allergies).
11. History of severe asthma or COPD.
12. BMI ≥30 kg/m^2 or <18 kg/m^2 at screening.
13. Active hepatobiliary disease or an AST or ALT >1.5 x ULN at screening or a total bilirubin >1.5 x ULN unless the subject has a history of Gilbert's disease.
14. Active infection or known history of Hepatitis B or C.
15. Positive serology for HIV at screening.
16. Evidence of previous TB infection (including BCG vaccination or positive PPD).
17. Other abnormal labs at screening:
    a. Platelets <100,000.
    b. Hgb <12 g/dL (males) or <11 g/dL (females).
    c. Fasting triglycerides >500 mg/dL.
    d. Estimated Glomerular Filtration Rate (GFR) <60 mL/min/1.73 m^2 (using MDRD calculator)
    e. Clinical lab value outside normal range, unless deemed as not clinically significant by the Investigator and Sponsor.
18. Sustained hypertension defined as average systolic ≥160 mmHg or diastolic ≥90 mmHg at screening.
19. 12-lead ECG findings demonstrating:
    a. QTc>450 msec for males or >470 msec for females at screening.

b. Any other abnormality that is clinically significant or is deemed as requiring further clinical evaluation by the Investigator.

20. Any history of unstable angina or Class 3 or 4 CHF, or any of the following diagnoses/conditions or procedures within the past year: stroke, myocardial infarction, life-threatening arrhythmia, major cardiovascular procedure (e.g., angioplasty, planned angioplasty, or carotid endarterectomy), or any other clinically significant cardiovascular disease diagnosis or procedure.
21. History of coagulopathy.

Exclusionary Procedures, Grafts, or Medication

22. Immunosuppressant therapy in the previous 30 days and/or requirements for chronic immunosuppressive therapy during the study as these may influence the expected action of the cells or graft.
23. Prescribed corticosteroid therapy above physiologic replacement doses in the previous 30 days.
24. Participation in a study of an investigational drug, device, or graft within five half-lives of the experimental agent or 30 days prior to enrollment in this study, whichever is longer.
25. Planned surgery in the general location of the implanted units (i.e., back and/or flank, arms, legs, abdomen, etc.) at any time during study participation.

Other

26. In the opinion of the Investigator, the subject is not suitable for the trial. This includes clinically significant medical and non-medical conditions, and/or psychiatric disorders.

The following additional exclusion criteria apply only to subjects with T1DM:

27. Use of any other diabetes-specific medication other than insulin (any preparation) or pramlintide.
28. A detectable stimulated serum C-peptide from either the Visit 1 lab evaluations or at any time-point during the 4-hour screening MMTT conducted at Visit 2, defined as >0.2 ng/mL (>0.0667 nmol/L).

4.3. Strategies for Recruitment and Retention

Sites will be evaluated and selected for study participation. Investigator database review may be used as recruitment procedures. If used, recruitment advertisements and retention materials will be approved by IRB/REBs prior to use.

4.4. Treatment Assignment Procedures

As this is an open-label study, subjects who meet the eligibility criteria will be enrolled into the trial on Day 1 and will have the VC-01 combination product surgically implanted on Day 1. The subject, sponsor, and site staff are not blinded and will know how many VC-01 units are being implanted depending on which cohort the subject enrolls into.

4.4.1. Enrollment Procedures

In Cohort 1, subjects will be enrolled to receive implantation of up to two VC-01-250 units and between four to six VC-01-20 or Comparator sentinel units.

After a minimum of three (and up to approximately 25) Cohort 1 subjects complete Visit 7 (Week 4), cumulative data will be compiled and reviewed by the independent DSMB. A DSMB approval will be required to continue to Cohort 2. Approximately 36 to 39 subjects will be enrolled into Cohort 2 and receive four or six VC-01-250 units as well as up to three VC-01-20 sentinel units implanted as described in Sections 3 and 5.

An electronic or paper-based system will be used to enroll subjects into the trial and will also be used as a method of tracking each of the units implanted into the enrolled subjects as each unit will have a unique number assigned.

4.5. Lifestyle Guidelines

Subjects will be instructed concerning the Lifestyle Guidelines described below at the times indicated in the Schedule of Assessments Table 1. In light of several of the items noted below which could impact clinic visit procedures, site personnel should remind subjects of these restrictions several days prior to their visits.

4.5.1. Dietary Restrictions

Subjects must abstain from all food and drink (except water) at least 10 hours prior to any blood sample collection for clinical lab tests and fasting glucose testing unless otherwise indicated.

Subjects who do not fast before a scheduled clinic visit will be required to return in a fasted state for a clinic visit within the specified visit window. Any scheduled assessments that do not require the subject to be fasting can be performed at the regularly scheduled clinic visit. Note: PROM questionnaires are completed under the same conditions at each visit. Therefore, if a subject does not fast before a scheduled clinic visit, the PROM questionnaires should not be administered.

Subjects will be counseled on appropriate dietary and lifestyle guidelines in accordance with local medical standards of care for T1DM or T2DM (as appropriate) at Day 1 (Visit 3) and will be asked to follow the advice throughout participation of the trial. Lifestyle guidance, including dietary guidelines, will be reinforced at all visits throughout the trial.

4.5.2. Exogenous Insulin Treatment and Administration

Subjects will remain on exogenous insulin therapy as appropriate to maintain blood glucose control throughout the duration of the study. Doses of exogenous insulin may be modified over the course of the study; however, as much as possible, the *types/brands* of insulin used by the subject should remain consistent. Also, the insulin injection delivery method for a subject (i.e., pump versus multiple daily injections) should not be changed without consulting the Sponsor and/or Medical Monitor. Subjects will be required to log their insulin doses every day.

Post-implantation, subjects must agree not to inject their exogenous insulin into the areas near the implantation sites. Additionally, while wearing the CGM sensor, subjects will not inject insulin within three (3) inches from the sensor site during sensor wear.

4.5.3. Physical Activity

For a week post-implantation, subjects will be asked to limit significant physical activity in order to ensure optimal healing of the incision sites (e.g., activities using large muscle groups in the implantation areas).

During the first four weeks post-implantation, subjects should avoid exposure to environments with temperature extremes (e.g., saunas, spas, ice baths, etc.)

Subjects should not perform physically strenuous exercise (e.g., heavy lifting, weight training) within 48 hours before each blood sample collection for clinical lab tests during the study. Moderate activities such as low-distance running, aerobics, bicycling, or swimming are examples of acceptable activities in the 48 hours preceding a clinic visit.

4.5.4. Alcohol, Caffeine and Tobacco

As part of good management of diabetes, the intake of alcohol should be limited (refer to exclusion criterion #7 for an acceptable amount of alcohol consumption).

Ingestion of caffeine will be prohibited for at least 30 minutes prior to the scheduled ECG and vital sign determinations.

Use of nicotine-containing products will be prohibited for at least 30 minutes prior to scheduled ECG and vital sign determinations.

4.5.5. Contraception

No women of childbearing potential will be allowed into the study. Only women of non-childbearing potential will be allowed to enroll into this trial.

All male (in conjunction with any female partner) subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually-active, must agree to use two acceptable methods of contraception consistently and correctly for the duration of the active treatment phase (i.e., while VC-01 is implanted). The subject will select the most appropriate method(s) of contraception from a permitted list (see below). The investigator or designee will instruct the subject in its consistent and correct use. The investigator or designee, at each study visit, will confirm and document consistent and correct use. In addition, the investigator or designee will instruct the subject to call immediately if the selected birth control method is discontinued or if a pregnancy is known or suspected in a male subject's partner. Acceptable methods of contraception include:

- Use of one of the following double-barrier methods: diaphragm with spermicide and a condom; cervical cap and a condom; or contraceptive sponge and a condom
- Use of hormonal contraception (any registered and marketed contraceptive agent that contains an estrogen and/or a progestional agent [including oral, subcutaneous, intrauterine and intramuscular agents, and cutaneous patches]) with one of the

following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; vasectomy; or IUD.

- Use of an IUD with one of the following: condom; diaphragm with spermicide; contraceptive sponge; vasectomy; or hormonal contraception (noted above).
- Vasectomy with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; IUD; or hormonal contraception (noted above).

4.5.5.1. Women – Non-childbearing Potential

To be considered as non-childbearing potential, women must meet at least one of the following criteria:

- Reached natural menopause (defined as ≥12 months of spontaneous amenorrhea in women >45 years of age, or ≥six months of spontaneous amenorrhea by subject verbal report with serum follicular stimulating hormone (FSH) levels in the postmenopausal range as determined by the central laboratory's reference range), or
- Had a hysterectomy and/or bilateral oophorectomy, or had bilateral tubal ligation or occlusion at least six weeks prior to Screening Visit 1 (Week -4).

4.5.6. Other Restrictions

Subjects should not undergo a magnetic resonance imaging (MRI) scan, computed tomography (CT) scan, or diathermy treatment while wearing the CGM sensor. The CGM, including the CGM sensor, should be removed before this type of procedure because of the magnetic fields and heat used in these treatments.

As additional data is gathered in this trial, there may be other restrictions implemented. These restrictions could be related to the efficacy or safety of VC-01. If required for safety reporting, the information will be communicated to sites as quickly as possible in order to inform the subjects and/or IRB/REB.

5. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

5.1. Study Product Description

5.1.1. Acquisition

PEC-01 drug substance is a cell population largely comprised of pancreatic progenitor and immature endocrine cells manufactured via directed differentiation of human embryonic stem cells (hESC). The CyT49 hESC line was derived by ViaCyte from an ethically-consented embryo in a process compliant with governing regulations.

5.1.2. Manufacturing, Formulation, Packaging, and Labeling

The CyT49 hESC line is the starting material for cell product manufacture. It is the only cell line being handled in the GMP manufacturing facility, and the cell line identity is assured via the quality process, batch records, and labeling. Tiered Master and Working Cell Banks have been

qualified. Additional manufacturing information is found in the Chemistry, Manufacturing, and Controls (CMC) section of the IND.

[redacted]

The PEC-01 and the Encaptra device comprise the VC-01 combination product being investigated in this trial. Note: the VC-01-250 combination product and the VC-01-20 sentinel units are made of the same components: PEC-01 and Encaptra device. The only difference between the two units is their size: the larger VC-01-250 unit is roughly half the size of a business card and the smaller VC-01-20 sentinel unit is roughly the size of a fingernail. Comparator sentinels are identical to the VC-01-20 sentinel unit except that they do not contain PEC-01 cells and may exclude specific storage medium excipients that are present in the VC-01 products. Sites are not blinded and will be aware of which units contain PEC-01 cells (VC-01-20 sentinels) and which units are Comparator sentinels.

[redacted] The packaging, labeling, and transport of the investigational units and sentinels will be outlined in a study reference manual. The VC-01 combination product arrives at the site fully-sealed and ready for implantation into the subject.

[redacted] The GMP cell manufacturing facility is qualified and licensed.

5.1.3. Product Storage and Stability

The shelf-life of the combined product [redacted] The "Use By Date" will be present on each unit.

The temperature of the product is maintained in a temperature-controlled, tested, and qualified environmental shipping container. [redacted]

5.1.4. Transport of Investigational Product to Site

The central manufacturing facility at ViaCyte will ship the investigational product and sentinels to the site where the surgeon investigator will perform the implantation. Units will be appropriately labeled and shipped, with each shipper containing implants for a single patient. The insulated product packaging used for shipping is capable of maintaining the target temperature range [redacted] for the duration of the shelf-life so it is recommended to keep all units within their environmental shipper cartons until just prior to implantation into the subject. The site will open the shipment to inspect the temperature logger and product package integrity. The site will contact ViaCyte immediately if there are noted irregularities or suspected damage to the product. **The suspect product should not be implanted into the subject without approval by the Sponsor.** ViaCyte or designee may wish to retrieve the damaged product and/or shipping containers so an appropriate evaluation can be done. After implantation, all environmental shippers and temperature loggers shall be returned to ViaCyte, Inc.

Further details will be outlined in a study reference manual.

5.2. Dosage, Preparation, and Administration of Product

Assuming the safety data from Cohort 1 support a dose increase, the subjects in Cohort 2 are anticipated to be implanted with four or six VC-01-250 units, which represents as much as a half log increase over Cohort 1. Furthermore, Cohort 2 subjects will receive up to three VC-01-20 sentinel units. It is estimated that each of the VC-01-250 units will contain approximately [redacted] It is anticipated that approximately 200,000 IEQ, equivalent to approximately 20% of normal beta cell mass, are required to achieve insulin independence.

The preparation of the investigational product at the site will be detailed in a study reference manual. Step-by-step guidelines on how to handle the units are specified in the manual.

The administration of the investigational product is performed by implantation on Visit 3 (Day 1). The implantation procedures follow step-by-step instructions which are outlined in a study reference manual. Site personnel will be expected to participate in a training program to ensure compliance with the product handling and implantation procedures.

5.3. Modification of Study Intervention for a Subject

Due to the nature of the product under investigation, “dose” adjustments (i.e., an increase or decrease) of the implanted VC-01-250 units are not permitted. However, at the discretion of the Sponsor and after consultation with the site investigator, or if a unit is suspected of malfunctioning or being damaged (Section 7.8), explantation of one VC-01-250 unit is allowed at any time post-implant for a subject.

Depending on the experience of each subject, the Investigator or subject may elect to have the subject withdrawn from the study and have the VC-01-250 units and all remaining VC-01-20 and/or Comparator sentinel units explanted.

Upon explantation of all remaining units at the conclusion of the subject's participation in the trial, if a unit is demonstrated to be malfunctioning and/or did not perform as expected, this observation will be documented and communicated to ViaCyte. Specific procedures relating to this topic will be outlined in a study reference manual.

5.4. Accountability Procedures

The VC-01-250 units and VC-01-20 and/or Comparator sentinels will be distributed to sites in preparation for implantation procedures on Enrollment/Day 1. The Investigator or designee must acknowledge receipt of the units either electronically or by hard copy. Unused or partially used supplies must be returned or destroyed, and accounted for as directed in a study reference manual. The Investigator is responsible for the accountability of all used and unused study supplies. There will be a system designed to track and manage the clinical supplies.

5.5. Assessment of Investigational Product Subject Compliance

As VC-01 is implanted into each subject, assessment of subject compliance with the investigational product does not apply.

If, however, the expected number of VC-01-20 and/or Comparator sentinels or VC-01-250 units is not implanted into a subject, this will be captured on a Case Report Form (CRF).

5.6. Concomitant Medications/Treatments

The surgeon or investigator, in consultation with the Sponsor, may prescribe concomitant medication or treatments [redacted] to be taken by the subject in order to aid with the implant healing and engraftment process. As additional data are gathered in this trial, changes in required concomitant medications and/or treatments may be necessary to enhance safety and/or efficacy of VC-01. The Sponsor will notify the sites and REB/IRB (if necessary) of such changes as the information becomes available.

All concomitant medications, treatments, and procedures will be captured on a CRF during study participation.

For details related to use of exogenous insulin, refer to Section 4.5.2.

6. STUDY SCHEDULE

The visit schedule for enrolled subjects is outlined in the Schedule of Assessments Tables as follows:

- Cohort 1 Subjects with T1DM: Table 1
- Cohort 2 Subjects: Table 2
- Cohort 1 Subjects with T2DM: Table 3

To minimize variability in the data, site personnel should attempt to schedule each subject's visits at approximately the same day of the week and the same time of day for that subject throughout the trial. For the procedures described below, where multiple procedures are scheduled at the same visit, the following chronology of events should be adhered to where possible:

- Patient-Reported Outcome Measure (PROM) instruments
- 12-lead ECG: obtain prior to vitals, blood samples
- Vital signs (sitting blood pressure, pulse, and temperature): obtain prior to blood samples
- Blood and urine samples
- Mixed Meal Tolerance Test (with associated blood draws). For any visits requiring both an MMTT and an explant procedure, it is acceptable to perform the MMTT on a separate day prior to the explant procedure, but no more than five (5) days prior to the explant procedure.
- Explant procedures: VC-01-20 and/or Comparator Sentinel units and VC-01-250 units. For all implanted sentinels in Cohort 1 and Cohort 2 subjects, the explants will occur at time-points to be determined by the Sponsor.

Other procedures: all other procedures may be obtained in any order either prior to blood samples or after; but not sooner than PROMs, ECG, or vitals.

Ultrasounds for the purpose of locating the implanted units prior to an explantation procedure may be done up to 3 days prior to the explantation.

In general, Cohort 1 subjects with T1DM and Cohort 2 subjects will follow the same schedule of assessments. There are slight differences in procedures relating to the number of sentinels implanted and explanted, and these items are noted below.

Cohort 1 subjects with T2DM will have up to13 study visits conducted over approximately seven (7) months following the schedule outlined in Table 3. For subjects with T2DM, the following study procedures are not applicable and can be disregarded where listed in Sections 6.1 through 6.17:

- PROM instruments
- MMTTs
- Continuous glucose monitoring (CGM)
- Diary completion

6.1. Screening Visit 1 (Week -4 to Week -3)

It is permissible for the screening visit to occur over several days. Subjects will be instructed to arrive at the site after an overnight fast in order to have the blood tests done at the Screening Visit. At this visit, the following procedures will be completed:

- Obtain informed consent (Note: it is acceptable for consent to be obtained prior to the screening visit).
- Collect demography, medical history including smoking status, alcohol frequency, and hormonal status, as well as prior and concomitant medications used.
- Obtain contact information for subject's health care provider and family members in order to reach subject if other contact methods are unsuccessful.
- Measure height and body weight; perform a complete physical exam including drug screen.
- Obtain a 12-lead ECG.
- Obtain vitals.
- Obtain fasting blood samples and urine specimens as outlined in the Schedule of Assessments. Provide subject with appropriate supplies to take home in preparation for the baseline urine sample to be taken on the morning of screening Visit 2 (Week -3).
- Conduct a simplified oral glucose challenge test (Section 7.13) to evaluate stimulated C-peptide.
- Site will review eligibility criteria to assess suitability for the trial. Note: if a lab value is outside the protocol-specified entry criteria, the site may bring the subject back to re-test that particular lab value without prior permission from the Sponsor.
- Review Lifestyle Guidelines.
- Contact the Sponsor to schedule provisioning of VC-01 for an implant procedure date. For additional details on the notification process, refer to the study reference manual.

6.2. Screening Visit 2 (Week -3 to Week -2)

Subjects appearing to meet eligibility criteria will return for Screening Visit 2 (Week -3). Subjects must be fasted for this visit. At this visit, the following procedures will be completed:

- Review eligibility criteria.
- Administer Patient-Reported Outcome Measure (PROM) instrument (DTSQs and ADDQoL). *Note: Not required for T2DM subjects.*
- Obtain weight/vitals.
- Obtain blood samples (according to the schedule of events); collect the urine sample from the first morning void taken at home [for albumin/creatinine ratio (this is the first of the duplicate baseline samples)]. Provide subject with appropriate supplies to take home in preparation for the second baseline urine sample.

- Perform 4-hour MMTT with blood draws at 0, 30, 60, 90, 120, 180, 240 minutes. This will serve as the baseline MMTT for the efficacy evaluations. *Note: Not required for T2DM subjects.*
- Provide CGM machine, supplies and provide instructions for use and care. It is recommended that the subject insert the sensor at the clinic. The site personnel should confirm the CGM equipment appears to be functioning appropriately prior to the subject leaving the clinic. *Note: Not required for T2DM subjects.*
- Provide Self-Monitoring of Blood Glucose (SMBG) portable meter, supplies, and provide instructions for use and care. Use of the meter provided by the Sponsor is required. *Note: Not required for T2DM subjects.*
- Provide study diary and instructions for use and care. This is where the subject will capture daily insulin doses, details on hypoglycemic event(s), and SMBG fingerstick values. **Remind subject that in order to remain eligible for the trial, daily compliance with entries between Visit 2 and 3 must be demonstrated.** *Note: Not required for T2DM subjects.*
- Assess AEs and concomitant medications.
- Contact the Sponsor to report any schedule changes or updates to the implant date. For additional details on the notification process, refer to the study reference manual.

The total Screening Period is expected to last approximately four weeks total. However, there may be situations in which an extension of the Screening Period beyond four weeks is warranted. If the Enrollment Visit 3 is scheduled to occur beyond five weeks (>35 days) of the occurrence of Screening Visit 1, sites should contact the Sponsor or designee before proceeding. Depending on the expected duration of the delay in conducting Visit 3, an Unplanned Visit may be required to perform certain, repeat screening procedures or the subject could be requested to undergo complete re-screening.

The total Screening Period may be accelerated, but a minimum of two weeks must elapse between Visit 2 and Visit 3.

6.3. Enrollment / Implantation Visit 3 (Day 1)

Subjects must be fasted for this visit. At this visit, the following procedures will be completed:

- Ensure entry criteria continue to be met
- Administer Patient-Reported Outcome Measure (PROM) instrument (DTSQs and ADDQoL). *Note: Not required for T2DM subjects.*
- Obtain weight/vitals.
- Perform an abbreviated physical exam.
- For a select group of subjects, obtain photographic documentation of the implantation sites (pre-implantation).

- Obtain blood samples per Schedule of Assessments, including immune panel and urine drug screen; collect the first morning void urine sample for albumin/creatinine ratio (this is the second sample for duplicate baseline samples required). ***Note***: The immune panel blood samples may be collected at any time between Visit 2 and Visit 3, once the subject's study qualification is confirmed (Section 7.12.2).
- Collect and review CGM, SMBG, and diary data and verify subject has demonstrated compliance with diary entries; dispense additional supplies. *Note: Not required for T2DM subjects.*
- Assess AEs and Concomitant Medications.
- Prepare subjects for implantation [see study reference manual]. The implantation procedure may be done at a separate location than the routine clinic visits.
- Implant VC-01-250 units and VC-01-20 and/or Comparator sentinel units (the number determined by the cohort into which the subject is enrolled).
- For a select group of subjects, obtain video documentation of the implantation procedure (see Section 7.5).
- Assess subject for up to four hours post-implantation for AEs.
- For a select group of subjects, obtain photographic documentation of the implantation sites (post-implantation).
- Upon release from the clinic, remind subject to limit significant physical activity in order to ensure optimal healing at implantation sites. Instruct the subject on the proper use of any post-implant treatments (e.g., compression garments).

6.4. Visit 4 (Day 2)

There is a +1 day window for this visit. At this visit, the following procedures will be completed:

- Perform a targeted physical exam focusing on the implantation site(s).
- Obtain weight/vitals.
- For a select group of subjects, obtain photographic documentation of the implantation sites.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues. *Note: Not required for T2DM subjects.*
- Assess AEs and concomitant medications.

Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation.

- Explant unit(s).

For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

Note: Laboratory assessments are not performed at this visit; therefore, the subject does not need to be in a fasted state.

6.5. Visit 5 (Day 5)

There is a +2 day window for this visit. At this visit, the following procedures will be completed:

- Perform a targeted PE focusing on the implantation site(s).
- Obtain weight/vitals.
- For a select group of subjects, obtain photographic documentation of the implantation sites.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues. *Note: Not required for T2DM subjects.*
- Assess AEs and concomitant medications.

Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation.
- Explant unit(s).
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

Note: laboratory assessments are not performed at this visit; therefore, the subject does not need to be in a fasted state.

6.6. Visit 6 (Week 2)

There is a ±2-day window for this visit. At this visit, the following procedures will be completed:

- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain blood samples.
- For a select group of subjects, obtain photographic documentation of the implantation site(s).

- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues. *Note: Not required for T2DM subjects.*
- Assess AEs and concomitant medications.

Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation.
- Explant unit(s).
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

6.7. Visit 7 (Week 4)

Note: After a minimum of three (and up to approximately 25) subjects in Cohort 1 have reached this Week 4 visit, all available data will be evaluated by the DSMB in order to trigger the enrollment phase of Cohort 2.

There is a ±3-day window for this visit. At this visit, the following procedures will be completed:

- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain blood samples (including immune samples). ***Note***: Ensure the collection time of immune panel samples meets requirements (Section 7.12.2).
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues. *Note: Not required for T2DM subjects.*
- Assess AEs and concomitant medications.
- Perform (safety) ultrasound assessment of implantation sites. For Cohort 1, this could be done with the (location) ultrasound assessment done prior to the explantation procedure. Note: If the ultrasound is performed on the day of the clinic visit, it must be done *after* the vitals, PE, and blood samples are collected.

Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation (and would include a safety assessment).
- Explant unit(s).

- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

6.8. Visit 8 (Week 8)

There is a ±7-day window for this visit. Subjects must be fasted for this visit. At this visit, the following procedures will be completed:

- Obtain weight/vitals.
- Obtain blood samples.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues. *Note: Not required for T2DM subjects.*
- Assess AEs and concomitant medications.
- Perform (safety) ultrasound assessment of implantation sites.
- Conduct a simplified oral glucose challenge test to evaluate stimulated C-peptide. Note: If the stimulated C-peptide result is measurable (≥0.1 ng/mL), perform a 2-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120 minutes) at an Unscheduled Visit as soon as possible. *MMTT not required for T2DM subjects.*

Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation.
- Explant unit(s).
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

6.9. Visit 9 (Week 12)

There is a ±7-day window for this visit. Subjects must be fasted for this visit. At this visit, the following procedures will be completed:

- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain blood samples (including immune samples) according to schedule of events. ***Note***: Ensure the collection time of immune panel samples meets requirements (Section 7.12.2).
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry;

provide counseling and assistance to subject if there are compliance issues. *Note: Not required for T2DM subjects.*

- Perform (safety) ultrasound assessment of implantation sites. If applicable, this could be done with the (location) ultrasound assessment done prior to the explantation procedure. Note: If the ultrasound is performed on the day of the clinic visit, it must be done *after* the vitals, PE, and blood samples are collected.
- Assess AEs and concomitant medications.

If the subject's stimulated C-peptide levels have remained immeasurable (<0.1 ng/mL) post-implant:

- Conduct a simplified oral glucose challenge test to evaluate stimulated C-peptide. Note: If the stimulated C-peptide result is measurable (≥0.1 ng/mL), perform a 2-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120 minutes) at an Unscheduled Visit as soon as possible. *MMTT not required for T2DM subjects.*

If the subject's stimulated C-peptide levels have been measurable (≥0.1 ng/mL) at any point post-implant:

- Perform 2-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120 minutes). *Note: MMTT not required for T2DM subjects.*

Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation.
- Explant unit(s).
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

6.10. Visits 10 and 13 (Weeks 16 and 39)

There is a ±7-day window for Visit 10. There is a ±14-day window for Visit 13. Subjects must be fasted for these visits. At these visits, the following procedures will be completed:

- Obtain weight/vitals.
- Perform a targeted PE if an explant was done at the previous visit.
- Obtain blood samples
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues. *Note: Not required for T2DM subjects.*
- Assess AEs and concomitant medications.

- *At Visit 13 only*, dispense supplies for the first morning urine void (to be brought to the clinic at Visit 14).

If the subject's stimulated C-peptide levels have remained immeasurable (<0.1 ng/mL) post-implant:

- Conduct a simplified oral glucose challenge test to evaluate stimulated C-peptide. Note: If the stimulated C-peptide result is measurable (≥0.1 ng/mL), perform a 2-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120 minutes) at an Unscheduled Visit as soon as possible. *MMTT not required for T2DM subjects.*

If the subject's stimulated C-peptide levels have been measurable (≥0.1 ng/mL) at any point post-implant:

- Perform 2-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120 minutes). *MMTT not required for T2DM subjects.*

Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation.
- Explant unit(s).
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

6.11. Visit 11 (Week 20)

There is a ±7-day window for Visit 11. Subjects must be fasted for this visit. At this visit, the following procedures will be completed:

- Obtain weight/vitals.
- Obtain blood samples.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues. *Note: Not required for T2DM subjects.*
- Dispense supplies for the first morning urine void (to be brought to the clinic at Visit 12).
- Assess AEs and concomitant medications.
- Perform (safety) ultrasound assessment of implantation sites. Note: if the ultrasound is performed on the day of the clinic visit, it must be done *after* the vitals and blood samples are collected.

If the subject's stimulated C-peptide levels have remained immeasurable (<0.1 ng/mL) post-implant:

- Conduct a simplified oral glucose challenge test to evaluate stimulated C-peptide. Note: If the stimulated C-peptide result is measurable (≥0.1 ng/mL), perform a 2-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120 minutes) at an Unscheduled Visit as soon as possible. *MMTT not required for T2DM subjects.*

If the subject's stimulated C-peptide levels have been measurable (≥0.1 ng/mL) at any point post-implant:

Perform 2-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120 minutes). *MMTT not required for T2DM subjects.*Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation.
- Explant unit(s).
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

6.12. Visits 12 and 14 (Weeks 26 and 52)

There is a ±7-day window for Visit 12. There is a ±14-day window for Visit 14. Subjects must be fasted for these visits. At this visit, the following procedures will be completed:

- Administer Patient-Reported Outcome Measure (PROM) instruments (DTSQs and ADDQoL at both Visits; DTSQc at Visit 14 only). *Note: Not required for T2DM subjects.*
- Obtain weight/vitals.
- Perform a complete PE (visit 12) or an abbreviated PE (visit 14).Obtain 12-lead ECG.
- Obtain blood samples (including fasting serum lipid panel and immune samples); obtain urine sample for albumin/creatinine ratio (on first morning void). ***Note***: Ensure the collection time of immune panel samples meets requirements (Section 7.12.2).
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues. *Note: Not required for T2DM subjects.*
- Perform (safety) ultrasound assessment of implantation sites. Note: If the ultrasound is performed on the day of the clinic visit, it must be done *after* the PROM, vitals, PE, and blood samples are collected.
- Assess AEs and concomitant medications.
- Perform 4-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120, 180, 240 minutes). *Note: Not required for T2DM subjects.*

For all subjects, activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation.
- Explant unit(s).
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

For T2DM subjects only:

- Visit 12 is the end-of-treatment visit. All remaining VC-01 units are to be explanted along with the completion of all other required procedures listed in Table 3.

6.13. Visits 15 and 17 (Weeks 65 and 91)

There is a ±14-day window for these visits. At this visit, the following procedures will be completed:

- Obtain weight/vitals.
- Obtain blood samples.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues.
- Dispense supplies for the first morning urine void (to be brought to the clinic at following visit).
- Assess AEs and concomitant medications.

Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation. Note: If the ultrasound is performed on the day of the clinic visit, it must be done *after* the vitals, and blood samples are collected.
- Explant unit(s).
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

6.14. Visit 16 (Week 78)

There is a ±14-day window for this visit. Subjects must be fasted for this visit. At this visit, the following procedures will be completed:

- Administer Patient-Reported Outcome Measure (PROM) instrument (DTSQs and ADDQoL).

- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain blood samples; obtain urine sample for albumin/creatinine ratio (on first morning void).
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Ensure subject continues to demonstrate compliance with the diary data entry; provide counseling and assistance to subject if there are compliance issues.
- Perform (safety) ultrasound assessment of implantation sites.
- Assess AEs and concomitant medications.

If the subject's stimulated C-peptide levels have remained immeasurable (<0.1 ng/mL) post-implant:

- Conduct a simplified oral glucose challenge test to evaluate stimulated C-peptide. Note: If the stimulated C-peptide result is measurable (≥0.1 ng/mL), perform a 2-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120 minutes) at an Unscheduled Visit as soon as possible.

If the subject's stimulated C-peptide levels have been measurable (≥0.1 ng/mL) at any point post-implant:

- Perform 2-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120 minutes).

Activities noted below to be performed only if an explant is planned for this visit:

- Perform ultrasound prior to planned explantation to locate the unit(s); the ultrasound can be performed up to 3 days prior to the explantation. Note: If the ultrasound is performed on the day of the clinic visit, it must be done *after* the PROM, vitals, PE, and blood samples are collected.
- Explant unit(s).
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).

6.15. Visit 18 (Week 104/Early Termination)

If a subject withdraws or is discontinued from the study at any time, the procedures outlined in Visit 18 (Week 104/Early Termination) should be performed and the subject will be followed in the 3-year, follow-up study (VC01-201).

All subjects will undergo an ultrasound to locate all remaining implanted units (VC-01-250 units and VC-01-20 and/or Comparator sentinel units). The ultrasound can be performed up to 3 days prior to the explantation and should include a safety evaluation of the remaining implanted units. Note: If the ultrasound is performed on the day of the clinic visit, it must be done *after* the PROM, vitals, PE, and blood samples are collected.

There is a ±7-day window for this visit. Subjects must be fasted for this visit. At this visit, the following procedures will be completed:

- Administer Patient-Reported Outcome Measure (PROM) instruments (DTSQs, DTSQc and ADDQoL). *Note: Not required for T2DM subjects.*
- Obtain weight/vitals.
- Obtain 12-lead ECG.
- For a select group of subjects, obtain photographic documentation of the explantation sites (pre-explantation).
- Perform a complete PE.
- Obtain blood samples (including fasting serum lipid panel, liver/CK, and immune samples); obtain urine sample for albumin/creatinine ratio (on first morning void). ***Note***: Ensure the collection time of immune panel samples meets requirements (Section 7.12.2).
- Collect all necessary study-related equipment.
- Review CGM, SMBG, and diary data; dispense additional supplies (if necessary). *Note: Not required for T2DM subjects.*
- Assess AEs and concomitant medications.
- Perform 4-hour MMTT in clinic with serial C-peptide measurements (0, 30, 60, 90, 120, 180, 240 minutes). *Note: Not required for T2DM subjects.*
- Prepare subject for explantation procedure (see study reference manual):
  - Explant all remaining VC-01-250 units.
  - Explant any remaining sentinel units.
- For a select group of subjects, obtain video documentation of the explantation procedure (see Section 7.5).
- For a select group of subjects, obtain photographic documentation of the explantation sites (post-explantation procedure).
- Review mandatory participation expectation for the 3-year, long-term, follow-up study (ICD process for follow-up study can be initiated. Please reference follow-up study Protocol VC01-201 for full details.)
- Remind subject of the follow-up visit 19 (Week 105).

6.16. Follow-up Visit 19 (Week 105)

There is a ±3-day window for this visit. All subjects, regardless of whether or not they completed the trial, will be seen in the clinic within one week following Visit 18/ET to follow-up on any unresolved AEs and to follow-up on the post-explantation experience.

- Obtain weight/vitals.

- Perform a targeted PE of explantation site(s).
- Assess AEs and concomitant medications.
- For a select group of subjects, obtain photographic documentation of the explantation site(s).

6.17. Unplanned Visits

Unplanned visits may occur at any time for reasons of subject safety and/or collection of additional time-point data. Possible reasons for unplanned visits include but are not limited to:

- Adverse event follow-up
- Abnormal laboratory test follow-up
- Review of blood sugar values with possible exogenous insulin dose adjustments
- Additional pre-operative evaluations
- Post-implant and/ or explant site evaluation (includes evaluation of incision healing)
- Suture removal post-procedure (if applicable)
- Repeat or follow-up ultrasound evaluations (safety or location)
- Explant of a VC-01-250 unit or sentinel unit
- Perform a simplified oral glucose challenge test
- Perform a MMTT in clinic with serial C-peptide measurements
- For a select group of subjects, obtain video documentation of the explantation procedure, if applicable (see Section 7.5)

Data will be collected at all unplanned visits depending on the type of visit conducted. Note: the subject must be in a fasted state if any of the following are to be collected or evaluated: lipid tests, fasting blood glucose measurements, MMTT, or PROM instruments.

7. STUDY ASSESSMENTS

Every effort should be made to ensure the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the Investigator that may make it unfeasible to perform a certain test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator or designee will document the reason for this and any corrective and preventive actions which will be taken to ensure that normal processes are adhered to as soon as possible.

Any instance of a protocol-required test not being performed at the required time, or within the protocol-described time window, will constitute a protocol deviation. These deviations will be captured and reviewed by the Sponsor or designee. Corrective actions will be put into place to prevent future occurrences of deviations, if possible.

7.1. Clinical Evaluations

7.1.1. Physical Examination

There are three types of physical exams that will be performed over the course of the study: complete, abbreviated, and targeted. Details of each are described below.

A **complete** physical exam will be performed by a physician or other medically-qualified health professional. The complete exams will be performed at screening Visit 1 (Week -4), Visit 12 (Week 26), and the final Visit 18 (Week 104 or early termination). The following body systems to be evaluated for the complete physical exam are: general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, abdomen, extremities, neurological, back/spinal/flank area, and lymph nodes. Results must be recorded in the subject's source documents and any significant findings on the screening physical exam must be recorded on the Medical History CRF. Over the course of the study, any clinically significant changes from the screening PE must be captured as AEs.

An **abbreviated** physical exam will also be performed by a physician or other medically-qualified health professional. The abbreviated physical exams will be performed at Visit 3 (Day 1), Visit 6 (Week 2), Visit 7 (Week 4), Visit 9 (Week 12), Visit 14 (Week 52), and Visit 16 (Week 78). The abbreviated exam includes assessment of the heart, lungs, abdomen, extremities, and skin [including implantation and/or explantation site(s)].

A **targeted** physical exam will be performed by a physician (either the PI or the site surgeon assigned to this protocol) or other medically-qualified health professional and will focus on the evaluation of the healing status at the implantation and/or explantation sites. The targeted physical exams will be performed at Visit 4 (Day 2), Visit 5 (Day 5), and Visit 19 (Week 105) in addition to any visit following a sentinel explant (e.g., Visit 10, Visit 13), inclusive of an unplanned visit if it is related to the post-surgical evaluation.

Other body systems should be evaluated as per the judgment of the Investigator or as needed to evaluate AEs. It is highly recommended that the same person conduct the same-type of physical exams for each subject over the course of the study.

7.1.2. Body Weight

Body weight will be measured using a standardized scale at each of the visits. Preferably, weight will be taken at approximately the same time of day, after voiding, and while wearing a gown or light clothing (no shoes or socks). Body weight should be reported in either pounds or kilograms. Scales are not being provided to each site. Subjects should be weighed on the same scale throughout the study.

7.1.3. 12-lead ECG

A single, supine 12-lead ECG will be obtained on the site's equipment at the times noted in the Schedule of Assessments. ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position and prior to the vital signs and blood collection but after the PROM questionnaires have been completed. The screening ECG will serve as the "baseline" ECG for comparison. All ECGs collected during the trial (planned and unplanned) should be

reviewed at the site for safety monitoring. The Investigator is responsible for retaining all copies of the ECG reports.

Any significant findings on the screening ECG must be recorded on the Medical History CRF. Over the course of the study, any clinically significant changes from the screening ECG must be captured as AEs.

7.1.4. Vitals: Sitting Blood Pressure, Pulse Rate, and Temperature

Vital sign measurements include a single measurement of sitting blood pressure, pulse rate, and temperature. BP and pulse rate should be measured on the site's equipment using either an automated device or a manual one. The following method should be used to record sitting blood pressure and pulse rate for subjects.

- Subjects will refrain from nicotine-containing products and/or ingesting of caffeine for at least 30 minutes prior to the measurements.
- Subjects should be seated in a chair with their backs supported, feet flat on the floor, and arms bared and supported at heart level.
- The appropriate cuff size must be used to ensure accurate measurement and used consistently throughout the study.
- Measurement should be taken on the same arm at each visit; preferably on the non-dominant arm.
- Measurement should begin after at least five minutes of rest.
- Assessment of pulse rate can be manual or automated; however, when done manually, the rate should be counted in the brachial/radial artery for at least 30 seconds.

Other procedures should not be performed during the time of the blood pressure and pulse rate measurements.

7.2. Mixed Meal Tolerance Test (MMTT)

A 4-hour standard mixed meal tolerance test (MMTT) after an overnight fast will be conducted during Visit 2 (Week -3). Additional 2- or 4-hour MMTT will be conducted at Visit 8 (Week 8), Visit 9 (Week 12), Visit 10 (Week 16), Visit 11 (Week 20), Visit 12 (Week 26), Visit 13 (Week 39), Visit 14 (Week 52), Visit 16 (Week 78), and Visit 18/ET (Week 104). Four-hour MMTT will be conducted at the following visits: Visit 2 (Week -3), Visit 12 (Week 26), Visit 14 (Week 52), and Visit 18 (Week 104). Two-hour MMTT will be conducted at all of the other visits only after a subject has a measurable C-peptide result ($\geq$0.1 ng/mL) from a simplified oral glucose challenge test post-implant (Section 7.13). For any visits requiring both an MMTT and an explant procedure, it is acceptable to perform the MMTT on a separate day up to 5 days prior to the explant procedure.

MMTTs are conducted after all other laboratory tests, PROM instruments, and vital signs evaluations have been collected. The MMTT test should be started prior to 10 AM. All MMTT supplies will be provided by the Sponsor or designee. Basal exogenous insulin will be continued during the test, but any short-acting insulin will be withheld starting

four hours prior to starting the test. Prior to initiating the MMTT, the subject's fasting glucose will be tested at the site, and the value must be within 70-200 mg/dL in order to begin the MMTT. If a subject's fasting glucose is not within range and the site feels as though it is reasonable to recheck, then one recheck can be done while the subject is in the clinic. If the subject's fasting glucose is not within the 70-200 mg/dL range, then s/he must return to the site within the visit window and attempt the MMTT again.

For convenience, an intravenous catheter can be placed in a patent vein in the subject's arm for the collection of blood samples. Insertion of the catheter should be performed at least 30 minutes prior to any blood collections on the days that the MMTTs will be performed.

Baseline blood samples will be drawn for measurement of glucose and C-peptide within approximately five minutes prior to the administration of the meal test. At time = 0, the subject will then be administered a standard meal consisting of one nutrition drink (Boost® Hi-Protein drink, 6 mL/kg body weight to a maximum of 360 mL) The entire amount of Boost® must be ingested within 15 min.

Additional samples for glucose and C-peptide are then collected at 30, 60, 90, and 120 minutes after the start of the Boost® meal test for the 2-hour MMTT (Weeks 8, 12, 16, 20, 39, 78) and at 30, 60, 90, 120, 180, and 240 minutes after the start of the Boost® meal test for the 4-hour MMTT (Weeks -2, 26, 52, 104).

The subjects should sit upright during the test. Slow walking is permitted, but vigorous exercise should be avoided.

MMTTs are not required for subjects with T2DM.

Further details will be outlined in the study reference manual.

7.3. Implantation Procedure

Implantation occurs at Visit 3 (Day 1). All subjects will have up to two or more primary VC-01-250 units and up to one (1) or more smaller sentinel units implanted. All units will be implanted in anatomical locations [redacted] suitable for implantation, as deemed appropriate by the Investigator and/or surgeon after consultation with the Sponsor.

For Cohort 1 subjects only, up to three (3) of the sentinels implanted in each subject may be a Comparator sentinel that does not contain PEC-01. Allowance for the implant of a Comparator sentinel unit may help identify the host response specific to the device and cellular components of VC-01 (Section 7.9).

Implantation will be executed [redacted] All medications administered during the implantation procedure are to be captured in the source documents and CRF. [redacted]

[redacted] Surgeons trained on the procedure will have discretion on the ultimate number and length of incisions. As much as possible, all implant procedures performed for subjects at one site should be conducted by the same surgeon.

A detailed description of the location for implantation and the surgical technique to be used for implantation will be provided as part of a study reference manual and site training. Site personnel are required to be trained on the implantation procedure and handling of all investigational product prior to the procedure.

Details on the surgical implantation and location of each implanted unit will be collected on a source document and reported on a CRF. Data collected from implantation surgeries and any explantation procedures will help inform the most appropriate implantation procedure to be followed [redacted]. As this is a FIH study, there is the possibility that the implantation procedures will be modified based on the data collected on Cohort 1 or Cohort 2 subjects. Updates to the surgical implantation procedures will occur as needed during the study and communicated to the sites to support the safety, tolerability, and efficacy profile of VC-01. If additional training to the sites is required, it will be provided.

[redacted] The subject will remain in the clinic for up to four hours following the procedure to monitor for AEs. Thereafter, release or extended observation of the subject is at the discretion of the surgeon and/or Investigator. Upon discharge, the subject should be reminded of the required Lifestyle Guidelines (Section 4.5).

Adverse events and the Investigator's assessment of causality to the implantation procedure (vs. the implanted product itself) will be captured when appropriate. For the week following the implantation, subjects will be advised to limit significant physical activity to ensure optimal healing at the implantation sites.

Within the first week following implantation, subjects will return to the clinic for Visit 4 (Day 2) and Visit 5 (Day 5). Clinical monitoring will be performed to identify and assess: bleeding, bruising, redness, localized swelling, and pain (discomfort). Additionally, subjects will be monitored for potential immunological reactions to the implantation by traditional symptoms and signs including: anaphylaxis, acute breathing problems (such as stridor caused by airway edema), angioedema, severe implantation site reactions at more than one site, diffuse and severe erythematous rash, diffuse and severe urticarial new onset multi-joint arthralgia or swelling. These events will be captured as AEs. If the Investigator suspects the subject might be having an immunological reaction, the Sponsor or its designee must be contacted immediately. Any additional pre- or post-operative evaluations or visits conducted beyond the protocol-specified study visits are at the discretion of the surgeon and/or Investigator and should be captured as an Unplanned Visit.

7.4. Photographs of Implantation and Explantation Sites

Photographic images may be obtained during the study on a small group of subjects to visually document the anatomical implantation and explantation sites immediately before and at various times after the procedures. It is expected that one or two sites will be selected to perform these assessments and that these assessments will occur with some or all of the subjects at the site(s).

Training and instructions for capturing the appropriate images in a standardized manner will be provided to the site(s) selected to participate in this activity. To maintain subject confidentiality, photographic images will be limited to the implantation and explantation sites and will not include any images of the subject's facial features or any other uniquely identifiable physical features. Photographs will be de-identified and may be uploaded to a central repository and used to refine the surgical procedure, site training, or other educational purposes related to the conduct of the clinical trial.

7.5. Video of Implantation and Explantation Procedures

Video images may be obtained during the study on a small group of subjects to visually document the implantation and explantation procedures. It is expected that one or two sites will be selected to capture video of the procedure and that these assessments will occur with only some of the subjects at the site(s).

To maintain subject confidentiality, video images will be limited to the implantation and explantation sites during the procedure and will not include any images of the subject's facial features or any other uniquely identifiable physical features. Video will be de-identified and uploaded to a central repository and used to refine the surgical procedure, site training, or other educational purposes related to the conduct of the clinical trial.

7.6. Ultrasound Monitoring

Ultrasound monitoring will be performed by trained personnel at the clinical site. The ultrasound evaluation will be performed using clinical-grade ultrasound machines. For consistency of results, it is recommended that the same evaluator at the site perform all of the ultrasound evaluations on a subject and that the same machine be used on a subject throughout the trial. Ultrasound monitoring will be required during the study and serves two purposes:

1. To monitor graft performance (safety evaluation); and
2. To pre-identify the anatomical location of the implanted units prior to an explantation procedure.

These purposes are discussed in more detail below.

Graft performance (safety) ultrasound monitoring:

[redacted]

The ultrasound images for safety evaluations will be captured, transmitted, and analyzed by a third-party, central imaging core lab.

- **Identify anatomical location of implanted units prior to explantation procedure**: Ultrasound evaluation will be performed around the time of any sentinel and/or VC-01-250 unit explantation (pre-explant) for surgical planning purposes. This will allow the explanting surgeon to minimize tissue trauma and reduce the likelihood of disturbing adjacent implants.

It is possible that the "safety" ultrasound procedure may correspond with the scheduling of the "anatomical location" ultrasound, and these investigations can be combined into one procedure. In addition, there will also be "safety" ultrasounds required which do not correspond to an upcoming explant procedure.

Early experiences in this study indicate the established ultrasound imaging procedure is successful at imaging implanted units and is appropriate for the purposes identified above. If modifications to the ultrasound procedure are considered necessary based on data collected over the course of the trial, the sites will be notified. Further information will be available in the imaging core lab manual and/or study reference manual.

7.7. Explantation of VC-01-20™ or Comparator Sentinel Units

VC-01-20 or Comparator sentinel units are co-implanted with the larger therapeutic VC-01-250 units.

In Cohort 1, between four (4) and six (6) VC-01-20 or Comparator sentinels will be implanted. Of these sentinel units, up to three (3) may be Comparator sentinels.

In Cohort 2, up to three (3) VC-01-20 sentinels will be implanted. The number of sentinels implanted in Cohort 2 will be determined by the Sponsor in collaboration with the site. The decision will be based on the available data from previous subjects as well as on the availability of anatomical space for surgical implantation.

All sentinel units will be removed at time-points to be determined by the Sponsor (refer to the Schedule of Assessments - Table 1, Table 2, and Table 3).

[redacted] A study reference manual will outline the sentinel explantation procedures to be performed by appropriately-

trained site personnel. The Sponsor or designee will provide training on the proper explantation technique.

The site should provide each subject with instructions on proper wound care and evaluation after sentinel explanation procedure, including a reminder to contact the site if any problems occur. As this is a FIH study, there is the possibility that the explantation procedures and techniques will be modified based on the data collected on Cohort 1 or Cohort 2 subjects. The Sponsor will communicate with the site surgeons to understand where improvements may be made. Updates will be communicated to other sites as appropriate. If additional training of the sites is required, it will be provided.

7.8. Explantation of VC-01-250™ Units

As outlined in the Schedule of Assessments (Table 1, Table 2, and Table 3), the VC-01-250™ units will be removed from all subjects at the end of the specified treatment period or earlier if the subject wishes to withdraw from the study, has a safety event which requires explant, or if the Sponsor/IRB/REB/DSMB/Regulatory Authorities stop the study.

At the discretion of the Sponsor and after consultation with the site investigator, or if a unit is suspected to be malfunctioning or damaged, explantation of one VC-01-250 unit is allowed at any time post-implant for a subject. Explant of one VC-01-250 unit may occur without requiring the subject to officially withdraw from the study (Section 13.6). [redacted] Although the sentinel units implanted in subjects are expected to behave similarly to the VC-01-250 units, an explant of a single VC-01-250 unit is permitted and will provide additional data on the status of graft function and cell performance.

[redacted] A study reference manual will outline the sentinel explantation procedures to be performed by appropriately-trained site personnel. The Sponsor or designee will provide training on the recommended explantation technique.

The site should provide each subject with instructions on proper wound care and evaluation after the VC-01-250 explantation procedure, including a reminder to contact the site if any problems occur.

As this is a FIH study, there is the possibility that the explantation procedures and techniques will be modified based on the data collected on Cohort 1 or Cohort 2 subjects. The Sponsor will communicate with the site surgeons to understand where improvements may be made. Updates will be communicated to other sites as appropriate. If additional training of the sites is necessary, it will be provided.

7.9. Histological Assessment of Sentinel Units and VC-01-250™ Units

All explanted VC-01-20™ and/or Comparator sentinel units and VC-01-250™ units will be placed in a fixative solution and immediately shipped back to ViaCyte or a designee for histologic assessment. Sample storage and shipping instructions will be provided to each site. Systematic histologic evaluation of the sentinel explants will help inform the team as to the expected performance of the larger implants (VC-01-250™ combination product) while the study is ongoing. Histological assessment of the units will be performed at ViaCyte or designee and may include but is not limited to:

[redacted]

The data from this evaluation may be captured in a separate database and described in a separate study report. The data may be used to optimize the implantation procedure, anatomical location of implants, or the perioperative care in conjunction with VC-01. Results from these assessments may be compared to the Sponsor's database [redacted].

7.10. Blood Glucose Monitoring

Throughout the trial, enrolled subjects will continue with concurrent exogenous insulin therapy as needed, and insulin requirements will be clinically managed and titrated as needed to maintain glycemic control throughout the study. For purposes of this study, the diary entries made by the subjects (e.g., insulin doses, SMBG fingerstick values, and HE occurrences) are the main source of information available to investigators to assist with treatment decisions.

T2DM subjects are not required to complete the study diary; therefore, treatment decisions are to be made based on the investigator's judgment and local standard of care**.** However, the SMBG supplies will be dispensed to the SSA subjects and utilized as applicable.

Blood glucose monitoring will be performed by various methods throughout the study to ensure proper glucose control:

- Laboratory tests at clinic visits (Sections 7.2 and 7.12)
- Continuous Glucose Monitoring (CGM) data (via CGM system provided to each T1DM subject).
- SMBG fingerstick via portable meter provided to each subject

Data from each of these methods will be reported via central laboratory, study diaries, and/or uploaded via computer technology. A study reference manual will outline the various logs and data collection portals.

Data collected from various sources from Visit 2 (Week -3) through Visit 3 (Day 1) will establish the baseline characteristics of each subject's diabetes pattern, (e.g. % time spent at

various blood glucose cutpoints via CGM data; SMBG fingerstick blood glucose levels, exogenous insulin doses, and frequency of hypoglycemic events).

During the study, decreasing requirements for exogenous insulin are expected to be achieved gradually, and are estimated to begin two to three months post implantation as cells differentiate into mature insulin-secreting cells. General contact, phone calls, and/or unplanned visits with the subject between visits are encouraged to facilitate insulin adjustments and to address any potential safety issues. In addition to Investigator review of fingerstick glucose values required per protocol, internal Sponsor review of blood glucose value data will be conducted routinely. If potentially concerning trends are seen for an individual subject, the Investigator will be notified and follow-up with the subject will occur if necessary.

7.10.1. Continuous Glucose Monitoring (CGM)

All T1DM subjects will be provided with a Continuous Glucose Monitoring (CGM) system. Subjects are required to wear their Sponsor-provided CGM during the 30-day period (window of ±seven days) prior to their scheduled clinic visits, although wearing of the CGM for the entire two-year study is encouraged.

All supplies and instructions on device use will be provided. Appropriately-qualified site personnel will instruct the subject on proper use and care at Visit 2 (Week -3) and as needed throughout the study. All subjects will be required to use the same Sponsor-provided CGM device in order to participate in the trial. The CGM device is configured to alert the subject in the event blood glucose values approach hypoglycemic levels.

At Visit 2 (Week -3), if the subject is unfamiliar with CGM, site personnel will be required to spend adequate time to ensure the subject understands the CGM and how to operate it. This training includes assisting the subject with the insertion of the sensor needle. Having previous experience with CGM is not a requirement of study entry, but all subjects are required to use CGM during study participation.

Data from the two weeks prior to appropriate clinic visits will be used in order to calculate the CGM endpoints (e.g., percent of time a subject's blood sugar is ≥180 mg/dL, ≥250 mg/dL, or ≤40 mg/dL, ≤50 mg/dL, ≤60 mg/dL, ≤70 mg/dL). Other endpoints using CGM data may be evaluated and, if so, will be described in the Statistical Analysis Plan (SAP).

In keeping with the labeled indication of the CGM device [redacted] being used in this trial, CGM data should not be used by the PI for treatment decisions, such as how much insulin subjects should take. The CGM system does not replace a SMBG meter. The subject should be encouraged and reminded to use the blood glucose values from the SMBG meter for insulin dosing decisions. The subject must record SMBG values, HE occurrence, and insulin dosing into the diary every day. This diary data must be reviewed by the site for completeness and in determining whether insulin dosing should be modified. Using the CGM sensor blood glucose readings for treatment decisions could lead to low or high blood glucose values. The CGM data for this trial will be used internally for secondary and exploratory endpoints. If CGM data is used at a site for an additional layer of diabetes monitoring, individual sites should determine how best to use available CGM data within the labeled indication.

T2DM subjects are not required to wear a CGM system during the study.

7.10.2. Self-monitoring Blood Glucose (SMBG)

Self-monitoring blood glucose (SMBG) supplies including a Sponsor-provided portable meter, test strips, lancets, control solution, and sharps containers will be provided and required for use. Instructions for SMBG monitoring at home via fingerstick and calibration of the portable meter will be provided to each subject. Recommended frequency for routine SMBG monitoring via fingerstick will be determined for each subject by the Investigator or designee.

SMBG log [includes records of any hypoglycemic events and accompanying symptoms (if any), fingerstick blood sugar measurements] and exogenous insulin dose logs will be completed via study diary by T1DM subjects only. For entries in the electronic tablet diary, data will be available for review in near real-time by the site staff via internet portal once synchronized through Wi-Fi by the subject. Based on entries made on the electronic tablet diary, e-mail alerts will be sent to the Investigator in the event a SHE is reported, or if the number of hypoglycemic events occurring within a seven (7)-day period requires further evaluation.

SMBG must be undertaken in the event that the subject believes he/she is experiencing symptoms of hyperglycemia or hypoglycemia such as: hunger, headache, dizziness, light-headedness, sweating, palpitations, tachycardia, tremulousness (shakiness), irritability, blurred vision, and disorientation etc., which cannot be reasonably explained by another cause (e.g., increased physical activity, skipped meal). Any confirmed (i.e., SMBG of ≤70 mg/dL) or unconfirmed (i.e., no SMBG value available) episode of hypoglycemia **must be captured by the subject** as soon as possible on the diary.

- For any severe hypoglycemic events (SHE) experienced between scheduled clinic visits, the subject must enter the data on the diary and also contact the study site to provide details of the event.

T2DM subjects are not required to enter HEs on a study diary, but in the event a T2DM subject experiences a HE, sites should collect the details of any HEs spontaneously reported by the subject and record on the CRF. If a T2DM subjects experiences a SHE, the subject must contact the study site to provide details of the event.

The site may request the subject return for an unplanned visit to review the glucose values and determine whether or not modifications in exogenous insulin dose are necessary in order to reduce the occurrence of hypoglycemic events. Investigators must review the hypoglycemic event information present on the diary, SMBG, glucose value trends, and exogenous insulin dose logs completed by the subjects at each study visit and must document this review in the subject source records. Based on this information, an assessment of any symptomatic occurrence of hypoglycemia must be undertaken, and the Investigator or the treating physician should make appropriate decisions regarding current insulin therapy dose regimen.

7.10.3. Definition and Classification of Hypoglycemic Events

All SMBG values of ≤70 mg/dL must be captured by the subject in the diary as a Hypoglycemic Event (HE). If a subject does not have an SMBG fingerstick value available but has symptoms of an HE, the HE must still be captured in the diary as an HE.

At each clinic visit, the Investigator or designee will review the subject-completed diary hypoglycemic event (HE) information, SMBG values, and any other supportive information.

Each hypoglycemic event occurring beyond Visit 2 must be captured on a CRF and will be will be classified given the definitions below. The investigator should still evaluate hypoglycemic events occurring between V1 and V2, but they are not captured on the CRF.

Severe hypoglycemic event (SHE): an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Documented symptomatic hypoglycemia: an event accompanied by typical symptoms of hypoglycemia with documented plasma glucose measured at ≤70 mg/dL (3.9 mmol/L).

Asymptomatic hypoglycemia: an event with measured plasma glucose of ≤70 mg/dL (3.9 mmol/L) in the absence of symptoms.

Probable symptomatic hypoglycemia: subject reports typical hypoglycemia symptoms but does not provide a temporally-associated SMBG value.

In addition to the hypoglycemia levels defined above, an additional category of "pseudo-hypoglycemia" will be noted.

Pseudo-hypoglycemia or relative hypoglycemia: an event is reported by subject, but the associated SMBG value is >70 mg/dL (3.9 mmol/L).

The frequency of these events will be captured and counted over the course of the study. In addition, the Sponsor will consider defining additional exploratory hypoglycemic events using the CGM data.

7.11. Patient-Reported Outcome Measurements

Patient-Reported Outcome Measure (PROM) instruments will be completed for all T1DM subjects while in a fasted state at select study visits throughout the study as noted in the Schedule of Assessments. Guidelines ensuring data quality will be optimized as suggested in the Food and Drug Administration (FDA) Guidance for Industry, "Patient-reported outcome measures: used in Medical product development to support labeling claims" [Dec 2009]. In order to minimize inconsistencies in the trial conduct, PROM instruments will be completed by the subject prior to any procedures being performed and administered via the study-provided medium.

Training and consistent instructions to subjects for these PROM instruments will be given. Specifically, the subjects will complete the PROM instruments in a quiet room and should answer each question without interruptions and independent of other external influences (e.g., spouse, site personnel, Investigator).

T2DM subjects are not required to complete the PROMs.

7.11.1. Diabetes Treatment Satisfaction Questionnaire (DTSQ)

This 8-item self-report scale assesses satisfaction with treatment for diabetes. There are two versions: DTSQs (original; "status" version) and the DTSQc ("change" version). Both versions were designed for use with individuals 16 years and older with type 1 or type 2 diabetes mellitus. Administration will take approximately five minutes. The constructs included in these instruments include treatment satisfaction (six items), perceived frequency of hypoglycemia (one item), and perceived frequency of hyperglycemia (one item) [REF 8, 9, 10].

On the DTSQs, subjects will provide ratings from six (very satisfied, convenient, flexible, etc.) to zero (very dissatisfied, inconvenient, inflexible, etc.). On the DTSQc, subjects will provide their ratings from +3 (much more satisfied now) to -3 (much less satisfied now). Hypo- and hyperglycemia items will be rated from zero (none of the time) to six (most of the time). The DTSQs will be administered at screening Visit 2 (Week -3), baseline Visit 3 (Day 1), Visit 12 (Week 26), Visit 14 (Week 52), Visit 16 (Week 78), and Visit 18 (Week 104). The DTSQc will be administered at Visit 14 (Week 52), and Visit 18 (Week 104/ET). The recall period will be no more than a few weeks for the DTSQs and up to 12 months for the DTSQc.

Sample copies of the DTSQs and DTSQc are provided in Appendix A and Appendix B. The actual questionnaires used in this study will be modified as appropriate (e.g., electronic format, protocol identifier, recall period). The questionnaire will be reviewed and approved by the IRB/REB before use.

7.11.2. Audit of Diabetes Dependent Quality of Life Questionnaire (ADDQoL)

The Audit of Diabetes Dependent Quality of Life Questionnaire (ADDQoL) is an individualized measure of the impact of diabetes on a person's quality of life.

The ADDQoL will be administered at screening Visit 2 (Week -3), baseline Visit 3 (Day 1), Visit 12 (Week 26), Visit 14 (Week 52), Visit 16 (Week 78), and Visit 18 (Week 104). A sample copy of the ADDQoL is provided in Appendix C. The actual questionnaire used in this study will be modified as appropriate (e.g., electronic format, protocol identifier, recall period). The questionnaire will be reviewed and approved by the IRB/REB before use.

7.12. Laboratory Evaluations

Sponsor-identified central laboratories, using a validated analytical method in compliance with the sponsor's standard operating procedures (when necessary), will assay all biological samples. The samples will be collected at the pre-specified time-points indicated on the Schedule of Assessments.

Clinical Laboratory Evaluations:

Subjects will have routine laboratory assessments performed throughout the study. The hematology assessments will include: hemoglobin, hematocrit, RBC count, platelet count, WBC count, total neutrophils, eosinophils, monocytes, basophils, and lymphocytes.

The chemistry assessments will include: BUN, serum creatinine, total calcium, sodium, potassium, chloride, bicarbonate, magnesium, phosphate, uric acid, ALT, AST, LDH, alkaline phosphatase, total bilirubin (direct and indirect bilirubin reflexively measured only when total bilirubin is greater than the ULN), creatine phosphokinase, albumin, and total protein.

> Note: If a subject demonstrates an ALT and/or AST values of >3 x ULN during the study, the subject will re-test every five to seven days until the values return to <3 x ULN. An ALT or AST value of >3 x ULN with total bilirubin ≥2 x ULN and alkaline phosphatase <2 x ULN will require re-testing every three to five days.

The fasting serum lipid panel assessments will include: total cholesterol, HDL-C, calculated LDL-C (Friedwald), triglycerides, VLDL. Non-HDL-C will be calculated as TC – HDL-C.

When triglycerides are >400 mg/dL, another sample will need to be collected from the subject and a directly measured LDL will be done.

Other assessments occurring at various times during the trial include but are not limited to: serum FSH (females at screening to determine childbearing status), fasting and stimulated C-peptide, HbA_{1c}, fasting glucose, urine pregnancy tests (at screening and when necessary), screening serology for HBsAg, HCV, HIV (1&2), and renal function evaluation via MDRD eGFR calculation.

Urinalysis (central lab dipstick): pH, protein, blood, ketones, leukocyte esterase, nitrites, with microscopy done if dipstick sample is positive for blood, nitrites, leukocytes, and/or protein. A bacterial culture and sensitivity will be done if nitrites or leukocyte esterase are positive. Another sample will need to be collected from the subject and submitted in order to perform the culture and sensitivity testing. At visits where a urine albumin/creatinine ratio is performed, the determination must be made on the first morning void.

7.12.1. Pregnancy Tests

Since no females of childbearing potential are allowed to enroll into the trial, a urine pregnancy test is administered at Visit 1, but is not included as a recurring procedure in the protocol Schedule of Assessments (Tables 1 and 2). However, pregnancy tests may be completed if the Investigator suspects a possible pregnancy, as per request of IRB/REB, or if required by local regulations. Additional information will be provided in a study reference manual.

7.12.2. Immune Panel

Blood samples for immunology-type tests will be obtained periodically throughout the trial: Visits 3 (Day 1), 7 (Week 4), 9 (Week 12), 12 (Week 26), 14 (Week 52), and 18/ET (Week 104). The immune panel of tests are listed below:

[redacted]

Blood samples will be sent to a central or third party lab with results sent to ViaCyte for possible inclusion in the clinical study database. The results of these tests will help inform ViaCyte's research and will not be provided to the clinical sites. If there is enough of a blood sample remaining on the collected samples, other immune function related tests may be performed, but no additional blood collection would be required. Fasting is not required prior to collection of these samples.

The cellular allo- and autoimmunity blood samples require additional processing prior to analysis that must be initiated within 24 hours of the collection time. If the additional processing cannot be completed onsite before being sent to the central laboratory, collection of the samples must

occur during afternoon hours. If needed, the samples can be collected on a day prior to the remainder of the visit in order to meet the requirements, but within the protocol-allowed visit windows. The baseline sample may be collected at any time between Visit 2 and Visit 3 once it has been determined the subject qualifies for the study. Additional details are provided in the central laboratory manual.

7.12.3. Reserve Blood Samples

Additional blood samples from subjects may be collected at baseline (Visit 3) and at up to four additional study visits for investigational assessment of biomarkers that could be associated with the cellular viability and durability of the implanted VC-01 product. The number of biomarkers assessed will be limited by the amount of sample available, but will not include any genetic testing. If the additional blood samples are collected, as much as 3 mL of blood could be collected at each time point. Results of these tests may not be reported to the site during the course of the study. Additional details of these tests will be provided in a separate laboratory manual.

7.12.4. Specimen Preparation, Handling, and Shipping

Details regarding the laboratory specimen preparation, handling, storage, and shipping procedures will be outlined in a separate laboratory reference manual.

7.12.5. Blood Volumes

For T1DM subjects, total blood collection volumes from visits requiring lab assessments are not planned to be greater than 750 mL over the course of the 2-year trial. Of the nineteen (19) clinic visits, there are four (4) visits where blood volumes are estimated to be up to approximately 95 mL: Visit 2 (Week -3), Visit 9 (Week 12), Visit 12 (Week 26), and Visit 14 (Week 52). Other visits, the blood volume required ranges from 0 mL to 55 mL.

If the reserve blood samples (Section 7.12.3) are collected, this would result in up to an additional 15 mL of blood collected over the 2-year trial.

For T2DM subjects there are fewer study visits and laboratory tests required. Total blood collection volumes from visits requiring lab assessments are not planned to be greater than 190 mL over the course of the 6-month trial. Of the 13 clinic visits, there are five (5) visits where blood volumes are estimated to be up to approximately 35 mL: Visit 1 (Week -4), Visit 3 (Day 1), Visit 7 (Week 4), Visit 8 (Week 8), and Visit 12 (Week 26). For other visits, the blood volume required ranges from 0 mL to 10 mL.

For all subjects, as noted in the Schedule of Assessments, blood collections are not planned to occur more frequently than once per week unless there is a need for an unplanned (safety) visit.

7.13. Simplified Oral Glucose Challenge Test

All subjects will be tested for evidence of a detectable (>0.2 ng/mL), stimulated C-peptide level via a simplified oral glucose challenge test at Visit 1. After Implantation Visit 3, the simplified oral glucose challenge test will be conducted at Visit 8 (Week 8), Visit 9 (Week 12), Visit 10

(Week 16), Visit 11 (Week 20), Visit 13 (Week 39), and Visit 16 (Week 78) until a measurable C-peptide result (≥0.1 ng/mL) is obtained.

For T1DM subjects, once a measurable C-peptide level is obtained, no additional simplified oral glucose challenge tests are required and the subject should instead follow the schedule for completion of the 2-hour MMTT (Section 7.2).

T2DM subjects will complete the simplified oral glucose challenge test regardless of C-peptide results.

After all fasting blood and urine samples required at the visit have been collected, at time = 0, the subject will then be administered a standard meal consisting of one nutrition drink (Boost® Hi-Protein drink, 6 mL/kg body weight to a maximum of 360 mL). The entire amount of Boost® must be ingested within 15 minutes. One blood sample for C-peptide is then collected at any time between 30 to 60 minutes after the start of the Boost® meal test.

8. SAFETY REPORTING

The Investigator is to report all directly observed AEs, all AEs spontaneously reported, or pregnancies by the study subject. In addition, each study subject will be questioned about AEs and pregnancies (if applicable) at each clinic visit.

8.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a product or medical device. Adverse events need not necessarily have a causal relationship with the treatment or usage.

Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs (changes from baseline status);
- Clinically significant changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease (includes worsening diabetes);

All observed or volunteered AEs regardless of suspected causal relationship to the investigational product will be reported as described in the following sections.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to ViaCyte or its designated representative and the site's IRB/REB. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. Follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and ViaCyte concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the Investigator to provide clarity and understanding of the event in the context of the clinical trial.

As required on the AE CRFs, the Investigator will use the National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Event (CTCAE) guidelines to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

MILD	Asymptomatic, or mild symptoms, clinical or diagnostic observations noted; intervention not indicated
MODERATE	Local or noninvasive intervention indicated
SEVERE	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
LIFE-THREATENING	Life-threatening consequences, urgent intervention indicated
DEATH	Death related to AE

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (medically significant) but would not be classified as serious unless it met one of the criteria for SAEs (See Section 8.2).

In addition, if the Investigator determines an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

All AEs will be reported on the AE page(s) of the CRF after Visit 2. It should be noted that the form for collection of SAE information may not be the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. AEs should be reported using concise medical terminology.

8.1.1. Causality Assessment of Adverse Events

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious). The Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product itself caused or contributed to an AE.

If the Investigator's final determination of causality is unknown, and the Investigator does not know whether or not the investigational product or surgical procedure caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the Investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

Relationship of an AE to the implanted units, the surgical implantation procedure and/or the explantation procedure will be assessed as follows:

Not related [unrelated or unlikely related]: A clinical event including laboratory test abnormalities without a temporal relationship to the investigational product exposure or the surgical procedures which makes a causal relationship improbable, and/or in which other drugs, chemicals, or underlying disease provides plausible explanations.

Possibly related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to exposure of the investigational product or the surgical procedures, but which could also be explained by concurrent disease or other drugs or chemicals.

Probably related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to the investigational product exposure or surgical procedures, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response.

8.1.2. Expected Adverse Reactions

As this is the first in human study, there are no definitive expected adverse reactions to this product, only hypothetical risks.

There are expected adverse reactions from the surgical implantation and explantation of the sentinels and VC-01-250 units and these are: localized procedural tenderness, pain, bleeding, itching, swelling, redness, and possible infection at the implant and explant sites.

Especially in Cohort 2 when the implanted cells are expected to begin to exert their physiologic action, there may be an increase in the number of hypoglycemic events noted before exogenous insulin doses are decreased. All events, whether they are expected or unexpected, will be captured as AEs and, if appropriate, SAEs.

8.1.3. Suspected, Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is a serious adverse reaction which is thought to be causally related to the investigational product or procedure and which is unexpected to occur. Reporting of SUSAR to the Sponsor or its designee, to the investigative sites, to the IRB/REBs and to the Regulatory Authorities during the trial is mandatory.

Because of the limited shelf-life of the investigational product, the results of continuous 14-day sterility testing of VC-01 are not available until after implantation occurs. In the unexpected event of positive culture results, the Sponsor will notify the PI, who will then notify the applicable subject. The Sponsor or designee will initiate further testing of the positive sample to identify the microorganism and conduct a root-cause analysis. The PI and Sponsor will evaluate any additional actions required to appropriately monitor the subject based on the results of the sample. If the medical condition of the patient is impacted as a consequence of the microorganism causing the positive sterility results, the event should be reported as a SUSAR within 15 days.

8.1.4. Unanticipated Problems

If there are unanticipated problems with the implantation and/or explantation of the units, these will be captured and reported to the Sponsor or designee so that further evaluation can be performed. As appropriate, unanticipated problems will be communicated to each site and to Regulatory Authorities by the Sponsor as appropriate. Each site will be responsible for reporting to the IRB/REB as appropriate.

8.1.5. Procedures to Be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the Investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.1.6. Adverse Events of Special Interest

Unexpected or premature explantation of sentinel or VC-01-250 units due to an AE are considered AEs of special interest. Also, subject-reported HEs will also be considered AEs of special interest. There may be additional data collected on these events.

Further instruction will be outlined in a study reference manual.

8.2. Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;
- Constitutes an Important Medical Event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Based on the definition above, severe hypoglycemic events (SHE) may or may not be reported as SAEs and will be left to the PI's discretion; however, they will need to be recorded on the hypoglycemic event (HE) CRF.

AEs reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room visits;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.2.1. SAE Reporting Procedures

If an SAE occurs, ViaCyte or designee will be notified within 24 hours of Investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to ViaCyte or designee must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the Investigator is obligated to pursue and provide information to ViaCyte in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by ViaCyte to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to ViaCyte or its designated representative.

8.2.2. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including SUSARs, will be carried out in accordance with applicable local regulations.

8.3. Reporting of Pregnancy

For investigational products, an exposure during pregnancy [also referred to as Exposure in Utero (EIU)] occurs if an enrolled female subject becomes, or is found to be, pregnant while in the study. In addition, if a male subject reports that his partner has become pregnant while he has had the VC-01 units implanted, this will also be captured as an EIU. Although women of childbearing potential are excluded from participating in this trial, the reporting procedures outlined in this section are provided as a precautionary measure.

Pregnancy itself is not an AE. However, adverse consequences of pregnancy should be reported as an AE/SAE.

If a study subject or a study subject's partner becomes or is found to be pregnant during the study, the Investigator must submit this information to ViaCyte or designee on an EIU Form. This must be done within 24 hours of awareness of the event. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy). All confirmed EIU cases and follow-up information will be reported in a Pregnancy Registry.

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify ViaCyte of the outcome as a follow-up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified, and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the Investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within one month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after one month should be reported as an SAE when the Investigator assesses the infant death as related or possible related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the Investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with a Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the EIU Form that the subject was given this letter to provide to his partner.

8.4. Reporting Period

For SAEs, including pregnancy reports, the active reporting period to the Sponsor or its designated representatives begin from the time that the subject provides informed consent through and including 28 days after explantation of all of the investigational product units. SAEs occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the investigational product are to be reported to the Sponsor.

AEs should be recorded on the CRF from Visit 2 (Week -3) through the last subject visit. At the conclusion of the trial, any ongoing AEs will be followed up on 28 days after the explantation procedure.

The reporting period for AEs/SAEs will overlap with the timing of the subject's participation in the mandatory 3-year follow-up study. Further details on the reporting of AEs spanning this VC01-101 protocol and the long-term follow-up protocol VC01-201 will be outlined in the separate follow-up protocol.

During the study, all subjects will have follow-up questions regarding their ongoing AEs at subsequent clinic visits. Depending on the reported event, there may be the need for the Investigator or designee to follow-up on AEs by phone with the study subject.

8.5. Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will meet at specified times throughout the study to review the accumulation of data. The DSMB will consist of at least 3 members, including a statistician. No Investigator involved in the trial or anyone connected to the Sponsor or participating vendors such as a CRO may be a member of the DSMB. Based on the review of the safety data, the DSMB may make recommendations regarding the conduct of the study. These may include, but are not limited to, amending safety-monitoring procedures, modifying the protocol or consent, terminating the study, or continuing the study as designed. The discussions and decisions of the DSMB will be summarized in written reports and provided to the Sponsor or designee. Where necessary, summary DSMB reports may be distributed to participating sites for submission to IRB/REBs. A separate DSMB Charter will direct the activities of the DSMB.

The approximate timing of DSMB meetings are noted below:

- After a minimum of three (and up to approximately 30) subjects from Cohort 1 have reached the Week 4 clinic visit and the results are available, the DSMB will meet. The available cumulative data collected in all subjects from Cohort 1 up until that time will be evaluated by the DSMB. The DSMB will make a recommendation based upon these findings to trigger the start of Cohort 2. The DSMB will not meet regularly during Cohort 1 unless there is a related AE that requires an independent DSMB review.
- At approximately 12-week intervals during Cohort 2's enrollment phase.
- Once the last subject has been enrolled in Cohort 2, the DSMB will meet approximately every six months until the last subject last visit has occurred.

Meetings of the DSMB may be added based on data review or by request.

8.6. Study Stopping Rules

If any of the following safety events are noted to occur in the study, an ad-hoc meeting of the DSMB will be requested. The DSMB will review the data and may recommend stopping the study for any of the following:

1. Two or more subjects have pronounced immune responses to the VC-01 combination product.
2. Two or more subjects experiencing an National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 treatment emergent adverse event (TEAE) in the same Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) considered to be possibly or probably related to the investigational product. TEAE is defined as an AE that starts on or after the date of implant surgery.
3. After a minimum of eight weeks post-implantation, there are two or more subjects who each experience two or more Severe Hypoglycemic Events (SHE) over a 6-month period unrelated to anything other than the VC-01-250 combination product. This also assumes that the SHE occurred despite reasonable reductions in the exogenous insulin requirements and appropriate dietary adjustments.
4. Two or more subjects develop serious AEs related to the implantation of the sentinels or therapeutic units; examples of such events are noted below:
    a. Development of an off-target cell growth (i.e., teratoma) within the unit which is noted on ultrasound and confirmed by pathologist.
    b. A related, severe, persistent, inflammatory response that does not resolve (e.g., severe site reactions, urticaria, erythematous rash, anaphylaxis, acute respiratory insufficiency, swelling).
5. Two or more subjects have an unexplained graft malfunction requiring explant.

In addition to the safety events noted above, the Sponsor may also decide to terminate the study for other safety or efficacy reasons. In the event that the study is terminated, all subjects will have their VC-01-250 units and sentinel units explanted and examined histologically, and all subjects will be followed for 3 years post-explant in a follow-up study (VC01-201).

In addition to these events, the DSMB will consider whether to recommend temporarily delaying enrollment in the trial for events considered by the Investigator to be related to the VC-01 combination product. The DSMB may also recommend that treatment continue for a shorter duration (i.e., less than the planned two years) or with a fewer number of implanted units. The DSMB may also recommend that the Sponsor close the study at any time in response to any legitimate safety concerns. The Sponsor will communicate DSMB recommendations to each site in a timely fashion. Each site's IRB/REB will make the ultimate decision to delay enrollment, modify treatment duration, or stop the study based on DSMB recommendations.

9. CLINICAL MONITORING

Routine monitoring of investigative sites by the Sponsor or designee will be done throughout the trial. The purpose of these monitoring visits is to inspect the facilities and various records of the trial.

The study monitor is responsible for inspecting electronic and/or online case report forms (CRFs) at regular intervals throughout the study to verify adherence to the protocol. During site

visits, the monitors will review source documents to confirm that the data recorded on CRFs are accurate. The monitor will ensure completeness and accuracy of the data and adherence to local regulations on the conduct of clinical research. The Investigator and institution will allow study monitors direct access to source documents to perform this verification. The Investigator and site staff agree to cooperate with the monitor to ensure that problems detected are appropriately addressed and resolved.

An associated monitoring plan will outline items to be monitored and the frequency of monitoring.

It is important that the Investigator(s) and relevant site personnel are available during the monitoring visits and possible audits or inspections by the Sponsor, designee, or Regulatory Authorities and that sufficient time is devoted to the process.

10. STATISTICAL CONSIDERATIONS

Methodology for the summarization and analysis of the data collected in this trial are given here and further detailed in a Statistical Analysis Plan (SAP), which will be maintained by ViaCyte. The SAP will be written and approved prior to the last subject in Cohort 2 passing the Week 26 visit, since this time-point will trigger a DSMB and Sponsor review of the accumulated efficacy and safety data.

The study SAP may modify what is outlined in the protocol; however, any major modifications of the endpoints or their analyses will be reflected in a protocol amendment.

The phrase "treatment group" is used in this section to denote the number of initially implanted VC-01-250 units. If a subject has a VC-01-250 unit explanted for any reason and remains in the study, then he/she will be included in the treatment group that is described by the number of VC-01-250 units originally implanted. If no VC-01-250 units are implanted, but sentinel units are implanted, then the subject will be included in the "0 implanted VC-01-250 units" treatment group.

All data from Cohort 1 T2DM subjects will be summarized separately from the T1DM subjects. As such, all information below pertains only to Cohort 1 T1DM and Cohort 2 (all T1DM) subjects.

10.1. Study Hypotheses

As this is a first-in-human study, there are no statistical hypotheses being tested.

10.2. Sample Size Considerations

At least three (3) and up to approximately thirty (30) T1DM subjects will be enrolled into Cohort 1. Thirty-six (36) to thirty-nine (39) subjects will be enrolled into Cohort 2, for a total enrollment between 39 and 69 T1DM subjects in both cohorts. Up to five (5) T2DM subjects may be enrolled as part of Cohort 1; this gives a total study enrollment up to 69 subjects.

A sample size [redacted] to detect a mean change from baseline to Week

26 in C-peptide $AUC_{0\text{-}4h}$ of 3.0 ng x hour/mL following an MMTT, assuming a standard deviation of 6.0. Other assumptions include a two-sided test with significance level of 0.05.

If the minimal level of detection for C-peptide is 0.20 ng/mL, this would give an AUC of 0.8 ng x hour/mL for the 4-hour MMTT. The same sample sizes [redacted] to detect a change from baseline to Week 26 in C-peptide $AUC_{0\text{-}4h}$ of 0.8 ng x hour/mL following an MMTT, assuming a standard deviation of 1.6.

For the 2-hour MMTT, sample sizes [redacted] to detect a change from baseline to Week 26 in C-peptide $AUC_{0\text{-}2h}$ of 0.4 ng x hour/mL following a MMTT (if the minimal level of detection for C-peptide is 0.20 ng/mL), assuming a standard deviation of 0.8.

There is no statistical analysis being conducted on data from T2DM subjects enrolled in the study. Therefore, no sample size assumptions are needed for the T2DM subjects. Note also that the data from the T2DM subjects will be summarized separately from that for the T1DM subjects.

10.3. Interim Analysis

No decision-making interim analyses (e.g., for early stopping for efficacy or futility, or for modification to the planned enrollment) are planned. A descriptive analysis may be produced when all subjects reach their Week 26 visit to support regulatory discussions. This report, if produced, will summarize key safety and efficacy endpoints for these subjects.

10.3.1. Safety Review

To help assess specific safety events in this FIH study and/or to evaluate the implantation and explantation techniques, the Sponsor or designee, Medical Monitor, and site surgeon(s) and/or Investigator(s) will maintain close communication during Cohort 1.

There will be an independent DSMB. Further information about the DSMB may be found in Section 8.5 of this protocol as well as the DSMB Charter, including specific descriptions of the scope of the members' responsibilities and the processes and definitions used to review and assess specific safety events.

Additional safety event adjudication committees may be established as appropriate. As described above, individual committee charters will provide specific descriptions of the scope of responsibilities and the processes and definitions used to review and assess specific safety events and to trigger the start of Cohort 2 enrollment.

10.3.2. Internal Efficacy and Safety Review

After the last subject in Cohort 2 passes Visit 12 (Week 26), cumulative data from all Cohort 1 and Cohort 2 subjects will be assembled and sent to the DSMB and Sponsor for review. If the Sponsor believes the efficacy data appear robust, and the DSMB believes the safety data are appropriate, the Sponsor may choose to proceed to an End-of-Phase 2 (EoP2) meeting with the FDA to discuss next steps.

10.4. Analysis Plan

The Analysis Plan detailed below pertains only to the T1DM subjects (T1DM subjects in Cohort 1, and all subjects in Cohort 2). The T2DM subjects in Cohort 1 will be summarized separately from the T1DM subjects, and will have their own Analysis Plan.

10.4.1. Analysis Populations

The Full Analysis Set (FAS) is the intent-to-treat (ITT) set of subjects. This set is defined as all T1DM subjects who were enrolled into the study and received implantation of at least one VC-01-250 or sentinel unit on Study Day 1. All efficacy summaries/analyses will be performed on the FAS. Subjects will be summarized by treatment group.

The Safety Analysis Set (SAS) will include all T1DM subjects who were enrolled into the study and in whom an implant surgery was attempted, regardless if any VC-01-250 units or sentinel-sized units were actually implanted. This includes all subjects in both Cohort 1 and Cohort 2. The SAS will be used for safety summaries.

10.4.2. Demographic and Subject Characteristics

Demographic information and subject characteristics such as gender, race, age, and baseline vital signs will be summarized. Pertinent medical history will also be summarized.

10.4.3. Primary Safety Analysis

Unless otherwise specified, the SAS (both Cohort 1 and Cohort 2 T1DM subjects who meet the SAS criteria) will be used for the primary safety summarizations. Adverse events and SAEs will be summarized by system organ class (SOC), by severity, and by relationship. This will be done by treatment group and overall. The summarization of AEs will focus on only those events that are TEAEs, but the AE listings will include all reported AEs regardless of when they started.

Other safety data, such as vital signs and clinical laboratory data will be summarized by study visit and treatment group. Where appropriate, change from baseline in safety data will also be summarized in a similar manner.

The number of subjects undergoing a premature VC-01-250 unit explant will be provided in a listing which includes the reason for explantation (i.e., safety issue, malfunction, damaged, planned explant, etc).

10.4.4. Primary Efficacy Analysis

Change from baseline in C-peptide $AUC_{0\text{-}4h}$ following an MMTT at Week 26 will be analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and baseline C-peptide $AUC_{0\text{-}4h}$ as a covariate. The FAS (both Cohort 1 and Cohort 2 T1DM subjects who meet the FAS criteria) will be used to analyze the primary efficacy endpoint. The output from the ANCOVA will include the least squares mean (LSM) and standard error (SE) for each treatment group.

10.4.5. Secondary Analyses

Each of the secondary efficacy endpoints will be analyzed using an $\alpha = 0.05$ level of significance. Given the large number of secondary efficacy endpoints, the p-values for these endpoints will be considered descriptive.

Unless otherwise specified, the FAS (both Cohort 1 and Cohort 2 T1DM subjects who meet the FAS criteria) will be used to analyze the secondary efficacy endpoints. Change from baseline in C-peptide $AUC_{0\text{-}4h}$ following an MMTT at Weeks 52 and 104 and change from baseline in C-peptide $AUC_{0\text{-}2h}$ following an MMTT at Weeks 8, 12, 16, 20, 26, 39, 52, 78, and 104 will be analyzed in a similar manner to the ANCOVA performed for change from baseline in C-peptide $AUC_{0\text{-}4h}$ at Week 26, with the relevant baseline as the covariate. For subjects who continue to have an immeasurable C-peptide (<0.1 ng/mL) as determined by the simplified oral glucose challenge test, the AUC of the respective 2-hour MMTT will be set to 0.

Change from baseline in average daily insulin dose in the seven days preceding clinic visits at Weeks 26, 52, 78, and 104, change from baseline in frequency of hypoglycemic events at Weeks 26, 52, 78, and 104, and change from baseline to Weeks 26, 52, 78, and 104, in PROM scores will be analyzed using ANCOVA, with treatment group as a factor and the relevant baseline as a covariate.

Time to onset of biological response of C-peptide following MMTT will be assessed using Kaplan-Meier (KM) curves, with the p-value from the logrank test also provided.

The percent of subjects who achieve exogenous insulin independence and the percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose at Weeks 12, 20, 26, 39, 52, 78, and 104 will each be analyzed using Fisher's exact test. The number and percent of subjects in each treatment group and the p-value from the Fisher's test at each time-point will be provided for exogenous insulin independence and for 50% reduction in average weekly exogenous insulin dose.

Unless otherwise specified, the SAS (both Cohort 1 and Cohort 2 T1DM subjects who meet the SAS criteria) will be used to summarize secondary safety endpoints. For the secondary safety endpoint of immune response as measured by serum immunoglobulin and hematological assays, any subject who appears to be having an immune response will have all relevant data described in a clinical narrative. In addition, data of interest from the assays may be summarized by treatment group and overall.

Changes in physical examinations will be summarized by treatment group and overall. Non-diabetic concomitant medications will also be summarized by treatment group and overall. Finally, implantation site assessments will be summarized at each time-point post-implantation and each visit thereafter. For each site assessment symptom, the number of subjects with the symptom at that time-point will be summarized by treatment group and overall.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

In compliance with ICH GCP guidelines, it is required that the Investigator and institution permit authorized representatives of the Sponsor or designee, regulatory agency(s), and the IRB or Canadian Research Ethics Board (REB) direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and/or reproducing any records and reports that are important for the evaluation of the study.

12. SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, Good Clinical Practice (GCPs) and applicable regulatory requirements, the Investigator and Institution should permit formal auditing by or on the behalf of the Sponsor, companies working with the Sponsor, and inspection by applicable regulatory authorities. The study site may be subject to review by their IRB/REB. Inspection of the site's facilities and review of study-related records may occur for any reason.

The Investigator and site staff agree to allow the auditors/inspectors to have direct access to source documents and study records for review, being understood that the personnel is bound by professional secrecy. The Investigator and site staff will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents. It is important that the Investigator and all relevant personnel are available during the audits or inspections and that sufficient time is devoted to the process.

If the Investigator is notified of a future inspection by regulatory authorities, s/he will inform the Sponsor or designee and authorize the Sponsor to participate in this inspection. The Investigator will immediately communicate to the Sponsor any results and/or information arising from the inspections by the regulatory authorities.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical Standard

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

13.2. Institutional Review Board (IRB) or Research Ethics Board (REB)

An IRB/REB must be constituted according to applicable requirements for each participating location.

It is the responsibility of the Investigator to have prospective, documented written approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/REB. All correspondence with the IRB/REB should be retained in the Investigator File. Copies of IRB/REB approvals should be forwarded to the Sponsor or designee.

The Institution shall have no ability to alter, amend or modify the protocol. The only circumstance in which an amendment may be initiated without IRB/REB and Sponsor approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB/REB and Sponsor in writing immediately after the implementation.

13.3. Informed Consent Process

The Investigator, or a person designated by the Investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The Investigator will retain the original of each subject's signed consent document and any amendments to the consent document. A copy of the signed consent form will be provided to the participant.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed and approved by the Sponsor (prior to use), approved by the IRB/REB, and available for inspection. The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

13.4. Exclusion of Women, Minorities, and Children (Special Populations)

Children will not be included in this trial. Each site will be encouraged to employ specific efforts to attract appropriate minority subjects and women of non-childbearing potential. However, women of childbearing potential will not be allowed to enroll since this is a first-in-human trial and the fetal effects are not known.

13.5. Subject Confidentiality

All data will be coded by number to protect confidentiality of subjects

Case Report Forms and other documents submitted to the sponsor should identify the subject by number only. Documents that are not for submission to Sponsor (e.g., source documents) should be kept in strict confidence by the Investigator. See also Section 11.

13.6. Reasons for Withdrawal

Investigators will make reasonable efforts to keep enrolled subjects in the study. However, if a subject is removed from treatment, a termination visit must be performed. This would generally include all procedures outlined in Visit 18 (Week 104) as well as the procedures outlined in follow-up Visit 19 (Week 105). Adverse events should be followed until their resolution.

Subjects may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the PI or Sponsor for safety or behavioral reasons.

There are subject-specific criteria and product-related criterion that will necessitate withdrawal from the study.

- After a minimum of eight weeks post-implantation, the subject experiences three or more Severe Hypoglycemic Events (SHE) over a six-month period unrelated to anything other than VC-01. This also assumes that the SHE occurred despite reasonable reductions in the exogenous insulin requirements and appropriate dietary adjustments.
- Subject has a new onset, off-target cell growth within the unit confirmed by a board-certified pathologist as a teratoma and is considered related to VC-01.
- Subject appears to mount an immune/inflammatory response that decreases or abolishes the performance of the graft and/or puts the subject at risk for immune reaction AEs. In this case, the Sponsor will assess the case fully (e.g., clinically and immune test results) and advise whether an explant of any units is advisable.
- Subject becomes pregnant.
- Subjects with a new diagnosis of rheumatoid arthritis or other autoimmune-type disease who begins a regimen of immunosuppressive therapies. Prior to withdrawing the subject, the site investigator should notify the Sponsor.
- Implanted units appear to be damaged or malfunctioning (e.g., localized infections, damaged unit, lack of efficacy). Note: In the case of a suspected malfunctioning or damaged unit, the Sponsor will assess the case fully and advise whether an explant of any units is advisable. Explant of one VC-01-250 unit may occur in this situation without requiring the withdrawal of the subject from the study upon request from the Sponsor.

If a subject meets any of these criteria, the VC-01-250 units and any remaining VC-01-20 and/or Comparator sentinel units will be explanted. The subject will be asked to follow-up with the study site for three (3) years post-explant in the long-term follow-up study.

13.6.1. Handling of Withdrawals

Subjects who are withdrawn from the study will have the VC-01-250 units and VC-01-20 and/or Comparator sentinel units explanted. If a subject withdraws from the trial and also withdraws consent for disclosure of future information in writing, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before withdrawal of consent.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. It is recommended that 3 attempts by telephone and at least 3 attempts by certified letter should be made. All attempts to contact the subject must be documented in the subject's medical record. Procedures will be put in place at each site to ensure that if a subject loses contact with the trial site, alternative measures will be utilized for the collection of information. This may

include contacting family members and health care providers and, when appropriate, using subject location services. In any circumstance, every effort should be made to document the subject's outcome, if possible, and to advise the subject to return to the clinic for explantation of VC-01-250 units and VC-01-20 and/or Comparator sentinel units.

Subjects who have not withdrawn consent, but who have been discontinued from the main study prematurely (with products explanted) will be rolled over into a 3-year, long-term, follow-up trial. Those subjects may initiate any other therapy as needed (prohibited medications will not apply to them).

For safety reasons, all early termination procedures (including explantation procedure) as described in Visit 18/ET and Visit 19 should be performed if a subject discontinues the trial.

13.7. Study Discontinuation

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response and recorded on the appropriate AE CRF page. The reason for study discontinuation will be documented.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements previously defined.

When a subject withdraws from the study, the units and remaining sentinels will be explanted and evaluated. The subject will be required to follow-up with the site and other health care professionals to ensure the appropriate insulin regimen is implemented.

13.8. Future Evaluation of Explanted Units

Evaluation of the explanted units is previously described. However, evaluated units will not be discarded, and there is the possibility of other future evaluations.

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Management Responsibilities

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study. A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

14.2. Data Capture Methods

The Investigator shall capture data in the form and manner required by the Sponsor. The Investigator has ultimate responsibility for the collection and reporting of all clinical and safety data entered on the CRFs and any other data collection forms (e.g., source documents) and ensuring that they are accurate, authentic, original, attributable, complete, consistent, legible,

timely (contemporaneous), enduring, and available when required. The Investigator or appropriate site personnel must sign (electronically or hard copy) the CRF(s) to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

14.3. Types of Data

In most cases, the source documents (the first recording of the data) are the hospital's or the physician's subject chart, laboratory reports, etc. The data collected on the CRFs must match the source data. Source documents also include, but are not limited to, the data captured by the subject in the study diary such as SMBG data, insulin dose logs, PROM instruments, and hypoglycemia event entries. There may be cases where the CRF, or part of the CRF, may serve as a source document. In these cases, a document should be available at the Investigator's site as well as at the Sponsor and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

It is expected that laboratory data (e.g., MMTT, CGM blood glucose data, ultrasound results, etc.), traceable to a particular subject, will be transmitted electronically to the study database in an ongoing manner during the study.

14.4. Study Records Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor and its designees, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, e-mails, meeting minutes, telephone calls, reports). The records should be retained by the Investigator according to International Conference on Harmonisation (ICH) local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to an independent third party arranged by the Sponsor.

The Investigator must obtain the Sponsor's written permission before disposing of any records.

14.5. Protocol Deviations

Every attempt to follow the protocol as written must be made. However, it is expected that there may be deviations resulting from circumstances beyond control or unintentional oversights or mistakes. These deviations from the protocol must be documented at the site, and the Sponsor must be notified. Depending on the particular IRB/REB used at each site, notification of the IRB/REB may be warranted as well.

15. DATA PROTECTION

The subject's protected healthcare information shall be treated in compliance with all applicable laws and regulations. When archiving or processing the protected healthcare information of the subjects, the Institution, Investigator, Sponsor and designees shall take all appropriate measures to safeguard and prevent access to these data by any unauthorized third party.

16. LITERATURE REFERENCES

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17. SUPPLEMENTS AND APPENDICES

Table 1: SCHEDULE OF ASSESSMENTS [COHORT 1 T1DM; N=3 to 30 SUBJECTS]

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 or ET	V19 Follow-Up
Assessments	**Wk -4**	**Wk -3**	**Day 1**	**Day 2**	**Day 5**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 26**	**Wk 39**	**Wk 52**	**Wk 65**	**Wk 78**	**Wk 91**	**Wk 104**	**Wk 105**
Visit Window				+1d	+2d	+/-2d	+/-3d	+/-7d	+/-7d	+/-7d	+/-7d	+/-7d	+/-14d	+/-14d	+/-14d	+/-14d	+/-14d	+/-7d	+/-3d
ICD	X																		
Entry Criteria	X	X	X																
Med Hx; Prior Meds	X																		
PROM administration [b]		X	X									X		X		X		X	
Physical Exam [c]	X		X	X	X	X	X		X	X		X	X	X		X		X	X
Height	X																		
Weight/Vitals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug screen	X		X																
Serology for HBsAg, HCV, HIV (1&2)	X																		
Hemat/Chem	X	X[d]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA1c	X		X						X			X		X		X		X	
FSH & UPT [e]	X																		
Fasting C-peptide	X																		
Stimulated C-peptide	X							X[f]	X[f]	X[f]	X[f]		X[f]			X[f]			
Dispense /Review CGM supplies and data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense /Review Diary Data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense/Review SMBG supplies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X																		
Urine albumin/creat		X	X									X		X		X		X	
Fasting serum lipid panel	X											X		X				X	

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 or ET	V19 Follow -Up
Assessments	**Wk -4**	**Wk -3**	**Day 1**	**Day 2**	**Day 5**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 26**	**Wk 39**	**Wk 52**	**Wk 65**	**Wk 78**	**Wk 91**	**Wk 104**	**Wk 105**
12-lead ECG	X											X		X				X	
4-hr MMTT/C-peptide & Glucose		X										X		X				X	
2-hr MMTT/C-peptide & Glucose								X[g]	X[g]	X[g]	X[g]		X[g]			X[g]			
Immune panel			X				X		X			X		X				X	
Reserve blood samples			X	X (up to four additional time-points as determined by Sponsor)															
Photographic documentation (in a select group of subjects)			X (2)	X	X	X												X (2)	X
Implant 2 VC-01-250 units			X (2)																
Implant 4 to 6 Sentinels			X (4-6)																
Explant Sentinel				X (up to 6 time-points; as determined by Sponsor)															
Explant VC-01-250 units [h]																		X (2)	
Ultrasound (safety) – unit evaluation and function [i]							X	X	X		X	X		X		X		X	
Ultrasound (pre-surgical) – identify unit locations [i]				X (time-points TBD based on explant procedures)														X	
Video (in a select group of subjects)			X	X (additional time-points TBD based on explant procedures)														X	
AE and Con Med	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ICD for 3-year follow-up study																		X	

a. Visit 1 (Week -4) screening procedures should preferably all occur on the same day with all results available prior to scheduling Visit 2 (Week -3) for subjects who appear to meet the eligibility criteria. There is no need to wait a full two weeks between Visit 1 and 2 if all results are available. Visit 4 (Day 2) has a +1 day window. Visit 5 (Day 5) has a +2 day window. Visit 6 (Week 2) has a ±2-day window. Visit 7 (Week 4) and Visit 19 (Week 105) have a ±3-day window. Visits 8, 9, 10, 11, 12, and 18 have a ±7-day window. All remaining visits have a ±14-day window. Clinic visits in which the subject must arrive in a fasted state are: Visit 1 (Week -4), Visit 2 (Week -3), Visit 3 (Day 1), Visit 8 (Week 8), Visit 9 (Week 12), Visit 10 (Week 16), Visit 11 (Week 20), Visit 12 (Week 26), Visit 13 (Week 39), Visit 14 (Week 52), Visit 16 (Week 78), Visit 18/ET (Week 104).

b. The DTSQs version will be administered at Visit 2 (Week -3), Visit 3 (Day 1), Visit 12 (Week 26), Visit 14 (Week 52), Visit 16 (Week 78), and Visit 18 (Week 104/ET). DTSQc version will be administered at Visit 14 (Week 52) and Visit 18 (Week 104/ET) only. The ADDQoL will be administered at Visit 2 (Week -3), Visit 3 (Day 1), Visit 12 (Week 26), Visit 14 (Week 52), Visit 16 (Week 78), and Visit 18 (Week 104/ET). Available electronic tablet diary data can be reviewed by the site staff as needed via a web-portal.
c. It is recommended that the same qualified site personnel complete these assessments for a subject at every visit throughout the study. Different types of Physical Exams will be performed throughout the study. Complete PE: Visit 1 (Week -4), Visit 12 (Week 26), Visit 18 (Week 104); Abbreviated PE: Visit 3 (Day 1), Visit 7 (Week 4), Visit 9 (Week 12), Visit 14 (Week 52), visit 16 (Week 78); Targeted PE performed at visits post implant and post explant and may include: Visit 4 (Day 2), Visit 5 (Day 5), Visit 10 (Week 16), Visit 13 (Week 39), Visit 19 (Week 105), and appropriate unplanned visits.
d. No hematology panel is evaluated at Visit 2. Only the chemistry panel will be tested at the central laboratory.
e. Only females of non-childbearing potential will be allowed enrollment.
f. The stimulated C-peptide should be obtained via the simplified oral glucose challenge test only if the subject's C-peptide levels remain immeasurable (<0.1 ng/mL) since implant.
g. The 2-hour MMTT should be performed only if the subject's stimulated C-peptide levels is measurable (≥0.1 ng/mL) since implant.
h. Explant of one VC-01-250 unit could occur prior to Visit 18 only at the discretion of the Sponsor (Section 7.8)

Ultrasounds will be done prior to any explantation procedure to determine the location of the implanted units. Subjects will have the ultrasound performed within a 3-day window to the scheduled explant of the VC-01-250 or VC-01-20 and/or Comparator sentinel units. When appropriate, the ultrasound performed prior to explantation is the same one done for safety reasons to measure possible lumen expansion.

Table 2: SCHEDULE OF ASSESSMENTS [COHORT 2; N=36 to 39 SUBJECTS]

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 or ET	V19 Follow-Up
Assessments	**Wk -4**	**Wk -3**	**Day 1**	**Day 2**	**Day 5**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 26**	**Wk 39**	**Wk 52**	**Wk 65**	**Wk 78**	**Wk 91**	**Wk 104**	**Wk 105**
Visit Windows				+1d	+2d	+/-2d	+/-3d	+/-7d	+/-7d	+/-7d	+/-7d	+/-7d	+/-14d	+/-14d	+/-14d	+/-14d	+/-14d	+/-7d	+/-3d
ICD	X																		
Entry Criteria	X	X	X																
Med Hx; Prior Meds	X																		
PROM administration[b]		X	X									X		X		X		X	
Physical Exam [c]	X		X	X	X	X	X		X	X		X	X	X		X		X	X
Height	X																		
Weight/Vitals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug screen	X		X																
Serology for HBsAg, HCV, HIV (1&2)	X																		
Hemat/Chem	X	X[d]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA1c	X		X						X			X		X		X		X	
FSH & UPT [e]	X																		
Fasting C-peptide	X																		
Stimulated C-peptide	X							X[f]	X[f]	X[f]	X[f]		X[f]			X[f]			
Dispense /Review CGM supplies and data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense /Review Diary Data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense/Review SMBG supplies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X																		
Urine albumin/creat		X	X									X		X		X		X	
Fasting serum lipid panel	X											X		X				X	

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 or ET	V19 Follow-Up
Assessments	**Wk -4**	**Wk -3**	**Day 1**	**Day 2**	**Day 5**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 26**	**Wk 39**	**Wk 52**	**Wk 65**	**Wk 78**	**Wk 91**	**Wk 104**	**Wk 105**
12-lead ECG	X											X		X				X	
4-hr MMTT/C-peptide & Glucose		X										X		X				X	
2-hr MMTT/C-peptide & Glucose								X[g]	X[g]	X[g]	X[g]		X[g]			X[g]			
Immune panel			X				X		X			X		X				X	
Reserve blood samples			X	X (up to four additional time-points as determined by Sponsor)															
Photographic documentation (in a select group of subjects)			X (2)	X	X	X												X (2)	X
Implant VC-01-250 units			X																
Implant VC-01-20 sentinels			X																
Explant VC-01-20 sentinel [h]				X (time-points as determined by Sponsor)															
Explant VC-01-250 units [i]																		X	
Ultrasound (safety) – unit evaluation and function [j]							X	X	X		X	X		X		X		X	
Ultrasound (pre-surgical) – identify unit locations [j]				X (time-points TBD based on explant procedures)														X	
Video (in a select group of subjects)			X	X (additional time-points TBD based on explant procedures)														X	
AE and Con Med	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ICD for 3-year follow-up study																		X	

a. Visit 1 (Week -4) screening procedures should preferably all occur on the same day with all results available prior to scheduling Visit 2 (Week -3) for subjects who appear to meet the eligibility criteria. There is no need to wait a full two weeks between Visit 1 and 2 if all results are available. Visit 4 (Day 2) has a +1 day window. Visit 5 (Day 5) has a +2 day window. Visit 6 (Week 2) has a ±2-day window. Visit 7 (Week 4) and Visit 19 (Week 105) have a ±3-day window. Visits 8, 9, 10, 11, 12 and 18 have a ±7-day window. All remaining visits have a ±14-day window. Clinic visits in which the subject must arrive in a fasted state are: Visit 1 (Week -4), Visit 2 (Week -3), Visit 3 (Day 1), Visit 8 (Week 8), Visit 9 (Week 12), Visit 10 (Week 16), Visit 11 (Week 20), Visit 12 (Week 26), Visit 13 (Week 39), Visit 14 (Week 52), Visit 16 (Week 78), Visit 18/ET (Week 104).

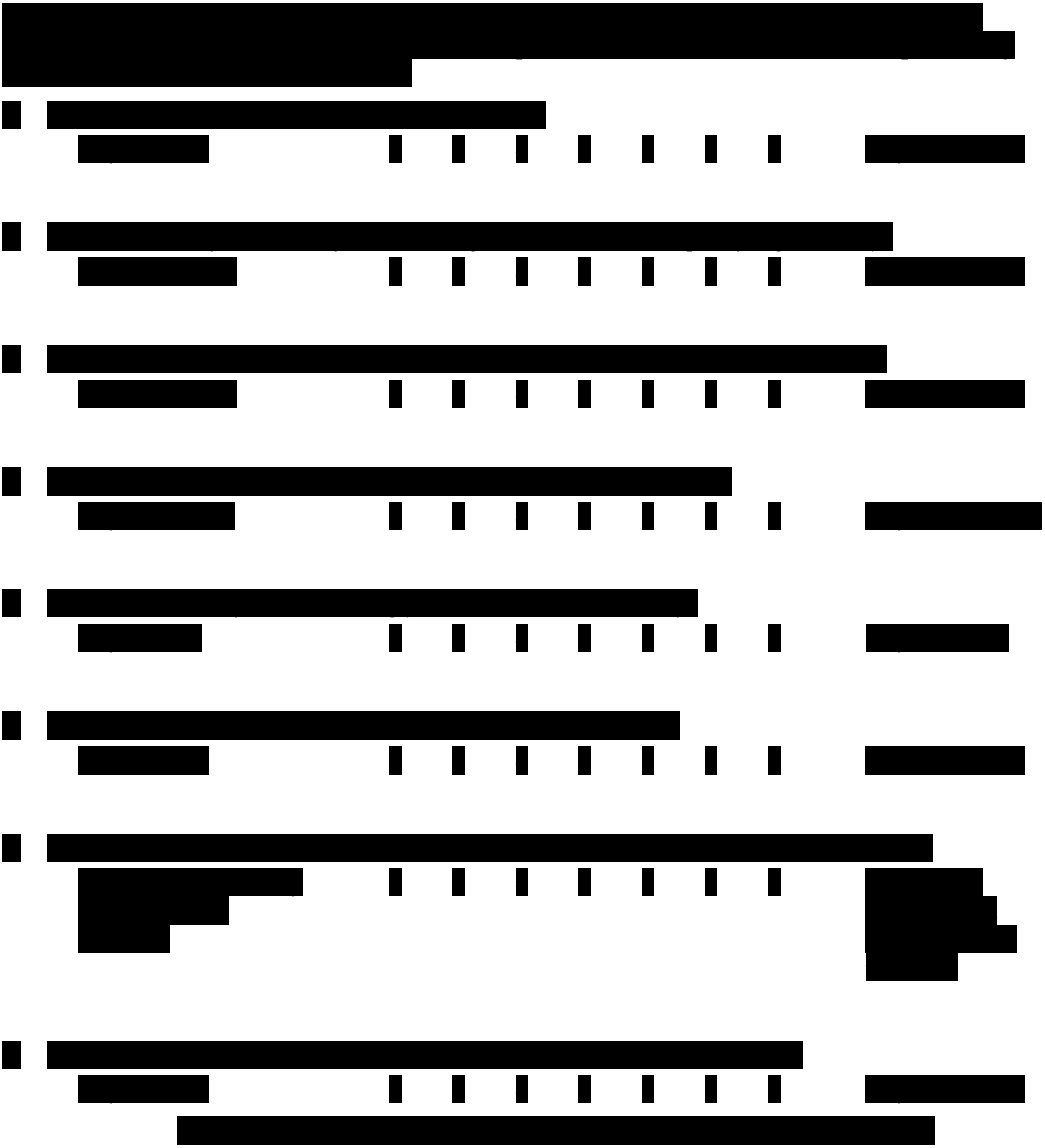
b. The DTSQs version will be administered at Visit 2 (Week -3), Visit 3 (Day 1), Visit 12 (Week 26), Visit 14 (Week 52), Visit 16 (Week 78), and Visit 18 (Week 104/ET). DTSQc version will be administered at Visit 14 (Week 52) and Visit 18 (Week 104/ET) only. The ADDQoL will be administered at Visit 2 (Week -3), Visit 3 (Day 1), Visit 12 (Week 26), Visit 14 (Week 52), Visit 16 (Week 78), and Visit 18 (Week 104/ET). Available electronic tablet diary data can be reviewed by the site staff as needed via a web-portal.
c. It is recommended that the same qualified site personnel complete these assessments for a subject at every visit throughout the study. Different types of Physical Exams will be performed throughout the study. Complete PE: Visit 1 (Week -4), Visit 12 (Week 26), Visit 18 (Week 104); Abbreviated PE: Visit 3 (Day 1), Visit 7 (Week 4), Visit 9 (Week 12), Visit 14 (Week 52), visit 16 (Week 78); Targeted PE performed at visits post implant and post explant and may include: Visit 4 (Day 2), Visit 5 (Day 5), Visit 10 (Week 16), Visit 13 (Week 39), Visit 19 (Week 105), and appropriate unplanned visits
d. No hematology panel is evaluated at Visit 2. Only the chemistry panel will be tested at the central laboratory.
e. Only females of non-childbearing potential will be allowed enrollment.
f. The stimulated C-peptide should be obtained via the simplified oral glucose challenge test only if the subject's C-peptide levels remain immeasurable (<0.1 ng/mL) since implant.
g. The 2-hour MMTT should be performed only if the subject's stimulated C-peptide levels is measurable (≥0.1 ng/mL) since implant.
h. As described in the protocol, up to three (3) VC-01-20 sentinel units are implanted in Cohort 2. The VC-01-20 sentinel units will be explanted at various time-points determined by the Sponsor.
i. Explant of one VC-01-250 unit could occur prior to Visit 18 at the discretion of the Sponsor (Section 7.8)
j. Ultrasounds will be done prior to any explantation procedure to determine the location of the implanted units. Subjects will have the ultrasound performed within a 3-day window to the scheduled explant of either the VC-01-250 or VC-01-20 units. When appropriate, the ultrasound performed prior to explantation is the same one done for safety reasons to measure possible lumen expansion.

Table 3: SCHEDULE OF ASSESSMENTS [COHORT 1 T2DM; N = Up to 5 SUBJECTS]

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12 or ET	V13 Follow -Up
Assessments	**Wk -4**	**Wk -3**	**Day 1**	**Day 2**	**Day 5**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 26**	**Wk 27**
Visit Window				+1d	+2d	+/-2d	+/-3d	+/-7d	+/-7d	+/-7d	+/-7d	+/-7d	+/-3d
ICD	X												
Entry Criteria	X	X	X										
Med Hx; Prior Meds	X												
Physical Exam [b]	X		X	X	X	X	X		X	X		X	X
Height	X												
Weight/Vitals	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug screen	X		X										
Serology for HBsAg, HCV, HIV (1&2)	X												
Hemat/Chem	X	X[c]	X			X	X	X	X	X	X	X	
HbA1c	X		X						X			X	
FSH & UPT [d]	X												
Fasting C-peptide	X												
Stimulated C-peptide	X							X	X	X	X	X	
Dispense SMBG supplies		X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X												
Urine albumin/creat		X	X									X	
Fasting serum lipid panel	X											X	
12-lead ECG	X											X	
Immune panel			X				X		X			X	
Reserve Blood Samples			X	X (up to four additional time-points as determined by Sponsor)									
Photographic documentation (in a select group of subjects)			X (2)	X	X	X						X (2)	X
Implant 2 VC-01-250 units			X (2)										
Implant 4 to 6 Sentinels			X (4-6)										
Explant Sentinel				X (time-points as determined by Sponsor)									
Explant VC-01-250 units [e]												X (2)[e]	
Ultrasound (safety) – unit evaluation and function [f]							X	X	X		X	X	
Ultrasound (pre-surgical) – identify unit locations [f]				X (time-points TBD based on explant procedures)								X	
Video (in a select group of subjects)			X	X (additional time-points TBD based on explant procedures)								X	
AE and Con Med	X	X	X	X	X	X	X	X	X	X	X	X	X
ICD for 3-year follow-up study												X	

a. Visit 1 (Week -4) screening procedures should preferably all occur on the same day with all results available prior to scheduling Visit 2 (Week -3) for subjects who appear to meet the eligibility criteria. There is no need to wait a full two weeks between Visit 1 and 2 if all results are available. Visit 4 (Day 2) has a +1 day window. Visit 5 (Day 5) has a +2 day window. Visit 6 (Week 2) has a ±2-day window. Visit 7 (Week 4) has a ±3-day window. Visits 8, 9, 10, 11, and 12 have a ±7-day window. Clinic visits in which the subject must arrive in a fasted state are: Visit 1 (Week -4), Visit 2 (Week -3), Visit 3 (Day 1), Visit 8 (Week 8), Visit 9 (Week 12), Visit 10 (Week 16), Visit 11 (Week 20), and Visit 12/ET (Week 26).
b. It is recommended that the same qualified site personnel complete these assessments for a subject at every visit throughout the study. Different types of Physical Exams will be performed throughout the study. Complete PE: Visit 1 (Week -4), Visit 12 (Week 26); Abbreviated PE: Visit 3 (Day 1), Visit 7 (Week 4), Visit 9 (Week 12); Targeted PE performed at visits post implant and post explant and may include: Visit 4 (Day 2), Visit 5 (Day 5), Visit 10 (Week 16) and appropriate unplanned visits.
c. No hematology panel is evaluated at Visit 2. Only the chemistry panel will be tested at the central laboratory.
d. Only females of non-childbearing potential will be allowed enrollment.
e. Explant of a VC-01-250 unit could occur prior to Visit 12
f. Ultrasounds will be done prior to any explantation procedure to determine the location of the implanted units. Subjects will have the ultrasound performed within a 3-day window to the scheduled explant of the VC-01-250 or VC-01-20 and/or Comparator sentinel units. When appropriate, the ultrasound performed prior to explantation is the same one done for safety reasons to measure possible lumen expansion.

APPENDIX A. DIABETES TREATMENT SATISFACTION QUESTIONNAIRE (STATUS) – DTSQs



APPENDIX B. DIABETES TREATMENT SATISFACTION QUESTIONNAIRE (CHANGE) – DTSQ$_C$

APPENDIX C. AUDIT OF DIABETES DEPENDENT QUALITY OF LIFE (ADDQOL)