VC02-101

AN OPEN-LABEL, FIRST-IN-HUMAN, STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF VC-02™ COMBINATION PRODUCT IN SUBJECTS WITH TYPE 1 DIABETES MELLITUS AND HYPOGLYCEMIA UNAWARENESS

Version 8, Amendment 9

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ViaCyte Inc.

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AN OPEN-LABEL, FIRST-IN-HUMAN, STUDY EVALUATING THE SAFETY, TOLERABILITY, AND EFFICACY OF VC-02™ COMBINATION PRODUCT IN SUBJECTS WITH TYPE 1 DIABETES MELLITUS AND HYPOGLYCEMIA UNAWARENESS

Protocol Number	VC02-101
Compound	PEC-01™ cells in a Delivery Device (together known as VC-02™ combination product)
Study Phase	1/2
Sponsor Name and Address	ViaCyte Inc. 3550 General Atomics Ct. San Diego, CA 92121
Version Number	8.0 (Amendment #9)

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PROTOCOL SUMMARY

Title:	An Open-Label, First-in-Human, Study Evaluating the Safety, Tolerability, and Efficacy of VC-02™ Combination Product in Subjects with Type 1 Diabetes Mellitus and Hypoglycemia Unawareness
Phase:	1/2
Population:	Subjects with type 1 diabetes mellitus (T1DM) and hypoglycemia unawareness (HU) will be enrolled into this first-in-human (FIH) clinical trial Cohort 1: At least three (3) subjects, but up to 15 total Cohort 2: Up to 60 subjects enrolled Total enrollment may be approximately 75 subjects
Number of Sites:	Approximately ten (10)
Study Duration:	The total duration of the trial is estimated to be up to 66 months: • Up to 42 months to complete enrollment of both cohorts • An additional 24 months from the time the last subject is enrolled in Cohort 2 until the last subject last visit
Subject Participation Duration:	Including Screening, Treatment, and Follow-up Visits, each subject's duration of participation is estimated as 110 weeks total (approximately two years). After all VC-02 units have been explanted, each subject will be required to be followed in a separate, long-term, follow-up study.
Description of Agent or Intervention:	ViaCyte has developed the VC-02 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-02 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, removable, Delivery Device (DD) designed to deliver and retain cells at the local implant site. Following subcutaneous implantation in anatomical locations involving the trunk or extremities, the VC-02 units are expected to vascularize adequately and the PEC-01 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-02-300 combination product for dose-finding, and smaller VC-02-20 combination product as sentinel units; these are smaller units that will be explanted at various time points and examined ex vivo. An immunosuppression regimen will be used to facilitate the engraftment and long-term function of implanted VC-02 units. The overall regimen may vary between subjects but may include the use of basiliximab, anti-thymocyte globulin (ATG), etanercept, sirolimus, tacrolimus, steroids and/or mycophenolate mofetil (MMF). Additional medications can be prescribed by the Investigator to increase the safety and efficacy potential of the product after consultation with the Sponsor.
Study Design:	This will be an open-label, FIH, clinical trial in subjects with T1DM and HU. Two cohorts are planned for enrollment in this trial: <u>Cohort 1 – Initial Safety and Tolerability</u>: Up to 15 subjects may be implanted with up to two (2) VC-02-300 units and up to six (6) VC-02 sentinels at one (1) or more clinical sites. If no VC-02-300 units are implanted in a subject, up to ten (10) VC-02 sentinels may instead be implanted. Sentinel units may be explanted at varying time points post-implant to assess the status of cell viability and differentiation, vascularization, and host response. At a minimum, the first three (3) subjects in Cohort 1 will be enrolled sequentially in order to assess safety and tolerability data at Week 2 before implanting the next subject. If no serious, treatment-related adverse events (AEs) are observed with the first three (3) subjects after each has reached Week 2, subsequent Cohort 1 enrollment may be performed in parallel. Total duration of treatment (implantation) may be up to two (2) years for each Cohort 1 subject, with the last unit explanted at Month 24. Cohort 1 subjects will complete a total of 18 study visits. After a minimum of three (3) subjects have been enrolled in Cohort 1 and have completed thru Week 4, the Data Safety Monitoring Board (DSMB) will review the cumulative Cohort 1 data for safety, tolerability, and proof of mechanism. <u>Cohort 2</u> – Up to 60 subjects will be implanted in cadres and will test a particular device configuration and/or implant strategy.

Based on information obtained from subject explants within a given cadre, the need for an alternate device configuration and/or surgical implant technique (e.g., pharmacological intervention, implant site, etc.) may be identified in order to improve engraftment and cell survival outcomes. These changes will be implemented prior to the next cadre of subjects commencing implantation to drive VC-02 engraftment optimization.

Cohort 2 subjects will be implanted with up to twelve (12) units. Of the twelve implanted units, no more than ten (10) will be VC-02-300 and the remainder will be VC-02-20 units. For example, if ten (10) VC-02-300 units are implanted in a subject, two (2) VC-02 sentinels may be implanted. Cohort 2 enrollment will be competitive across approximately ten (10) sites. Sentinel units may also be explanted at various time points post-implant.

Total duration of treatment may be up to two (2) years for each Cohort 2 subject, with the last unit explanted at Month 24. Cohort 2 subjects will complete a total of up to 18 study visits.

Study Objectives:

Objectives: This trial will test whether VC-02 combination product can be implanted and maintained with safety, tolerability and efficacy for up to two years. There are two cohorts in this FIH trial with the following study objectives.

Cohort 1 study objectives:

- Assess the local and systemic safety and tolerability of VC-02 combination product when implanted into subjects with T1DM and HU.
- Assess histological proof of mechanism for VC-02 combination product (e.g., cell survival and differentiation to beta cells).

Cohort 2 study objectives:

- Evaluate the clinical efficacy and further assess safety and tolerability of VC-02 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.

Exploratory objectives:

- Optimize the recommended surgical implantation procedure, anatomical location, and perioperative care for VC-02.

- Assess the effects of the host immune response to implanted VC-02 units

Primary Endpoints:

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

- Cohort 1: Targeted safety and tolerability profile inclusive of:
  - The incidence of AEs with causality related to VC-02 combination product, the surgical procedures required for VC-02 administration, and the immunosuppressive drug regimen.
  - The incidence of off-target growth as evidenced by implanted VC-02 units via lumen ultrasound measurements, or by histological examination of explants.
  - The incidence of immune sensitization defined by presence of donor anti-HLA antibodies absent prior to implant.
  - Implant tolerability assessments (e.g., fever, erythema, pain, tenderness, induration) for up to four hours post-implantation and at subsequent visits.
- Cohort 2: Change from baseline to Week 26 in C-peptide $AUC_{0\text{-}4h}$ following a Mixed Meal Tolerance Test (MMTT)

Secondary Endpoints:

Safety and Tolerability: Comprehensive profile of VC-02 combination product implanted for up to two years as measured by:

- All reported AEs
- The incidence of immune sensitization defined by presence of donor anti-HLA antibodies absent prior to implant
- Implant tolerability assessments (e.g., fever, erythema, pain, tenderness, induration) for up to four hours post-implantation and at subsequent visits
- The incidence of subjects requiring a premature explant due to safety, tolerability, or malfunction issues

Efficacy:

- Change from baseline to Weeks 16, 26, 39, 52, 78, and 104 in average daily insulin dose in the seven days preceding the Clinic Visit

	• Percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose from baseline to Weeks 16, 20, 26, 39, 52, 78, and 104 • Percent of subjects who achieve exogenous insulin independence; of those subjects achieving insulin independence, the percent achieving HbA1c <7.0% • Percent of time spent with blood glucose values at various cut points (e.g., <54 mg/dL, ≥54 to <70 mg/dL, ≥70 mg/dL to ≤180 mg/dL, and >180 mg/dL) as measured by each subject's continuous glucose monitoring (CGM) device • Change from baseline to Weeks 16, 26, 39, 52, 78, and 104 in time-in-euglycemic range (≥70 mg/dL to ≤180 mg/dL), time-in-hypoglycemic ranges (<54 mg/dL and ≥54 to <70 mg/dL), and time-in-hyperglycemic ranges (>180 mg/dL) as measured by each subject's CGM
Exploratory Endpoint:	Histological results of explanted units and any associated tissue capsule as evaluated for cell viability, vascularization, immune response, and/or cell maturation and differentiation.
Inclusion Criteria:	• Signed and dated informed consent form • Men and non-pregnant women of 18-65 years of age • Diagnosis of T1DM for a minimum of five (5) years • At least one severe hypoglycemic event, or for patients with CGMs, documentation of a low blood glucose value <54 mg/dL (<3.0 mmol/L), in the previous 12 months • Documented hypoglycemia unawareness (Clarke score ≥4) or significant glycemic lability as assessed by the Investigator • Stable, optimized diabetic regimen for at least 3 months • Insulin dosage at screening <1 unit/kg/day • Willing to use a provided CGM System • Willing and able to comply with daily entries on a study diary • All male subjects and female subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception until final explant. For further details of contraceptive requirements for this study, please refer to Section 5.4.5

Exclusion Criteria:

- A detectable stimulated serum C-peptide at any time-point during the Screening period, defined as >0.2 ng/mL (>0.0667 nmol/L)
- Use of any oral diabetes-specific medication
- Medical history of islet cell, kidney, and/or pancreas transplant
- Occurrence of six or more severe, unexplained hypoglycemic events within six months of enrollment
- Uncontrolled or untreated thyroid disease or adrenal insufficiency
- Known causes of diabetes other than T1DM
- Diabetic complications such as severe kidney disease or renal dysfunction, proliferative retinopathy, diabetic foot ulcers, amputations attributable to diabetes, and/or severe peripheral neuropathy
- Non-compliance with current anti-diabetic regimen
- Hemoglobin A1C level of ≥10.0%
- Significant skin conditions involving the area(s) targeted for implantation
- Alcohol abuse
- Positive urine drug screen for substances of abuse at screening or enrollment visit, medical marijuana use may be allowed by the PI after consultation with the Medical Monitor and/or Sponsor
- Prior history of malignancy with the exception of:
    - Basal cell carcinoma of the skin;
    - Squamous cell carcinoma of the skin that has been recurrence free for ≥five years;
    - Appropriately treated in situ carcinoma of the cervix
- Known allergies to portions of the cellular excipients used as cell preservation solution or the PEC-01 manufacturing process (i.e., bovine, porcine allergies)
- History of severe asthma or COPD
- BMI ≥32 kg/m2 or <18 kg/m2 at screening

- 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
- Active infection or known history of Hepatitis B or C or HIV
- Evidence of previous TB infection (including BCG vaccination or positive PPD)
- Negative serostatus for Epstein-Barr virus
- Other abnormal labs at screening:
    - Platelets <100,000
    - Hgb <12 g/dL (males) or <11 g/dL (females)
    - Fasting triglycerides >500 mg/dL
    - Estimated Glomerular Filtration Rate (GFR) <60 mL/min/1.73 m2 (using MDRD calculator)
- Clinical lab value outside normal range, unless deemed as not clinically significant by the Investigator and Sponsor
- Sustained hypertension defined as average systolic ≥160 mmHg or diastolic ≥90 mmHg at screening
- 12-lead ECG findings demonstrating:
    - QTc>450 msec for males or >470 msec for females at screening
    - Any other abnormality deemed clinically significant requiring further clinical evaluation by the Investigator
- 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
- History of coagulopathy
- 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
- 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

Statistical Considerations

Sample Sizes – Cohorts 1 and Cohort 2

- Sample size in Cohort 1 was empirically derived, based upon safety considerations and data accumulated from previously performed ViaCyte clinical trials. A sample size of up to 15 subjects should allow for adequate assessment of Cohort 1 study objectives.
- A sample size of 60 subjects in Cohort 2 will enable staggered enrollment of cadres of subjects allowing for testing of alternate device configurations and/or surgical implant technique (e.g., pharmacological intervention, implant site, etc.) in order to improve engraftment and cell survival outcomes. This approach will drive VC-02 engraftment optimization.

Sample Size – Primary Efficacy Endpoint

- Once the optimized device configuration and surgical implant technique is determined, a sample size of 40 subjects implanted [redacted]

  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. A sample size of 40 subjects [redacted]

  For the 2-hour MMTT, a sample size of 40 subjects [redacted]

Analysis Populations

- The Full Analysis Set (FAS) is defined as Cohort 2 subjects enrolled into the study and who received implantation of at least one VC-02 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 Cohort 1 and Cohort 2 subjects enrolled into the study and in whom

an implant surgery was attempted, regardless if any VC-02 units were actually implanted.

Primary Safety

- The SAS 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-02-300 unit explant will be provided in a listing which includes the reason for explantation.

Primary Efficacy

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

Table 1. SCHEDULE OF ASSESSMENTS

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17 or ET	V18 Follow-Up
Assessments	**Wk -5**	**Wk -4**	**Day 1**	**Day 2**	**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		**+14d**		**+1d**	**+/- 2d**	**+/-3d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 14d**	**+/- 14d**	**+/- 14d**	**+/- 14d**	**+/- 14d**	**+/- 7d**	**+/- 3d**
Informed Consent	X																	
Entry Criteria	X	X	X															
Med History / Prior Meds	X																	
12-lead ECG	X										X		X				X	
Physical Exam (Complete)	X										X		X				X	
Physical Exam (Abbreviated)			X		X	X		X				X			X			
Physical Exam (Targeted)				X														X
Height	X																	
Weight / Vitals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clarke Survey	X								X		X	X	X		X		X	
Immunosuppression Drug Dosing		X (adjust dosing as needed)																
Dispense / Review CGM Data		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	
Dispense / Review SMBG Supplies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Implantation Procedure			X															
Explantation Procedure				X (time-points as determined by Sponsor)													X	

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17 or ET	V18 Follow-Up
Assessments	**Wk -5**	**Wk -4**	**Day 1**	**Day 2**	**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**
Ultrasound - Safety Evaluation							X		X		X		X		X		X	
Ultrasound - Pre-Explant[a]				X (time-points TBD based on explant procedures)													X	
Video and Photos[b]			X	X (additional time-points TBD based on explant procedures)													X	
AE and Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ICD for Follow-Up Study[c]																	X	
Central Laboratory Tests or Study-Provided Testing Kits																		
Drug Screen[d]	X		X															
HBsAg, HCV, HIV	X																	
CMV IgG and IgM[g]		X											X				X	
CMV PCR		X						X			X							
EBV IgG	X																	
Hematology & Chemistry	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA1c	X		X						X		X		X		X		X	
Follicular Stimulating Hormone	X																	
Urine Pregnancy Test[e]	X		X										X				X	
Thyroid Stimulating Hormone[f]	X																	
Quantiferon TB	X																	
SOGCT C-peptide	X																	
Ultrasensitive C-peptide[h]		X					X	X	X	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 or ET	V18 Follow-Up
Assessments	**Wk -5**	**Wk -4**	**Day 1**	**Day 2**	**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**
2-hr MMTT/C-peptide & Glucose							X	X	X	X		X		X		X		
4-hr MMTT/C-peptide & Glucose		X									X		X		X		X	
Urinalysis	X																	
Urine Albumin/Creatinine		X									X		X		X		X	
Fasting Lipid Panel	X										X		X				X	
Immune Panel		X				X			X		X		X				X	
Reserve Blood Samples	X										X		X		X		X	
Local Laboratory Tests																		
Immunosuppression Drug Levels & Safety Panels				X (frequency as described in Section 7.11.3)														

a. Pre-explant unit location ultrasound only required at the discretion of the Investigator. Unit location may be determined via palpation depending on anatomical location (Section 7.7).

b. Video and/or photographs of the surgical procedure or implantation anatomical locations are to be captured only if requested by the Sponsor but are otherwise not required.

c. A separate consent document will be provided to the subject for the follow-up study.

d. The Visit 1 drug screen sample will be analyzed at the central lab. The Visit 3 drug screen is to be conducted locally using the study-provided kit.

e. The urine pregnancy test is administered locally using the study-provided kit. Visit 3 results must be available before the implant procedure commences. Visit 17 test should occur on the same day as the final explantation procedure.

f. FSH testing only required for post-menopausal women who are not using contraception.

g. CMV IgM is not tested at Visit 2 (only IgG). CMV IgG and IgM testing is performed at Visit 13 and Visit 17 only if previous test results were negative.

h. Ultrasensitive C-peptide samples to be collected in conjunction with MMTTs pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.

INVESTIGATOR'S AGREEMENT

By signing this protocol, I confirm that I have read and agree to conduct the trial as outlined herein, complying with the obligations and requirements of clinical investigators and all other requirements listed in the Code of Federal Regulations.

_____

Principal Investigator's Name (printed)

_____ _____

Principal Investigator's Signature Date

DECLARATION OF SPONSOR

This clinical study protocol was subject to critical review and has been approved by the sponsor. The information it contains is consistent with:

- ***The current risk-benefit evaluation of the investigational product***
- ***The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP as described in the Code of Federal Regulations and according to applicable local requirements.***

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

May 18, 2020

Howard Foyt, MD, PhD, FACP

Vice President, Clinical Development

Chief Medical Officer

Date

REVISION HISTORY

Version Number	Version Date
1.0	08 November 2016 (Original) **never implemented*
1.1	01 March 2017 (Amendment #1 – United States Only) **never implemented*
1.2	15 March 2017 (Amendment #2 – United States Only)
2.0	31 July 2017 (Amendment #3 – United States Only)
3.0	17 October 2017 (Amendment #4 – United States Only)
4.0	29 November 2017 (Amendment #5 – Canada Only)
5.0	24 July 2018 (Amendment #6)
6.0	11 October 2019 (Amendment #7)
7.0	18 March 2020 (Amendment #8 – Belgium Only)
8.0	18 May 2020 (Amendment #9)

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
ATG	Anti-Thymocyte Globulin
AUC	Area Under the Curve
BCG	Bacillus Calmette-Guerin
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CGM	Continuous Glucose Monitoring
CHF	Congestive Heart Failure
CMV	Cytomegalovirus
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
DD	Delivery Device
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr Virus
EC	Ethics Committee
ECG	Electrocardiogram
EDDS	Encaptra® Drug Delivery System
EIU	Exposure in Utero
EoP2	End of Phase 2
ET	Early Termination
FAS	Full Analysis Set
FBGC	Foreign Body Giant Cell
FDA	Food and Drug Administration
FIH	First-in-Human
FSH	Follicular Stimulating Hormone

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GFR	Glomerular Filtration Rate
HbA1C	Hemoglobin A1C
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein Cholesterol
HE	Hypoglycemic Event
hESC	Human Embryonic Stem Cell
HIV	Human Immunodeficiency Virus
HLA-PRA	Human Leukocyte Antigen Panel Reactive Antibody
HU	Hypoglycemia Unawareness
IB	Investigator Brochure
ICD	Informed Consent Document
ICH	Internal Conference on Harmonisation
IEQ	Islet Equivalent
IFU	Instructions for Use
IUD	Intrauterine Device
KM	Kaplan Meier
LDH	Lactate Dehydrogenase
LDL-C	Low Density Lipoprotein Cholesterol
LSM	Least Squared Method
LST	Lymphocyte Stimulation Test
MDRD	Modification of Diet in Renal Disease
MLR	Mixed Lymphocyte Reaction
MMTT	Mixed Meal Tolerance Test
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DD	Delivery Device
PE	Physical Exam
PEC	Pancreatic Endoderm Cells

PI	Principal Investigator
PPD	Purified Protein Derivative
PT	Preferred Term
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SE	Standard Error
SHE	Severe Hypoglycemic Event
SMBG	Self-Monitoring Blood Glucose
SOC	System Organ Class
SOGCT	Simplified Oral Glucose Challenge Test
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
VC-02	VC-02™ Combination Product
VLDL	Very Low-Density Lipoprotein

1. INTRODUCTION

1.1. Background Information and Scientific Rationale

Diabetes mellitus, defined by the loss of metabolic glycemic control, is a tremendous healthcare issue. While exogenous pharmaceutical insulin and adjunct medicines can alleviate hyperglycemia, and when managed properly, prevent serious life-threatening excursions in blood glucose levels, it is far from a perfect solution. The natural history of type 1 diabetes mellitus (T1DM) presents acute and chronic health risks to all affected patients. Controlling the disease with insulin self-administration carries the acute risk of hypoglycemic events (HE) and even death, and the need for constant vigilance and testing results in a significant degradation of quality of life for the patient (and often, their families). Moreover, controlling the short-term challenges of diabetes with monitoring and insulin does not prevent the serious long-term sequelae of diabetes. These long-term sequelae include microvascular complications, such as peripheral and autonomic neuropathies, nephropathies, retinopathy, and diminished wound healing, as well as macrovascular complications and cardiovascular disease.

Certain subgroups of T1DM patients have increased risks associated with hypoglycemia due to the relative absence of physiological symptoms associated with low blood glucose, also known as hypoglycemia unawareness (HU). Additionally, subgroups of patients who experience wide swings in blood glucose levels also are at particular risk of severe hypoglycemia. It has been reported that as many as 10% of patients with T1DM fall into this high-risk category (Ryan, et al., 2004). Further, as many as 50% of insulin-dependent diabetes mellitus patients at 15 to 20 years post-diagnosis report having lost their ability to perceive the autonomic symptoms associated with low blood sugar. Severe hypoglycemia has been reported to occur six to seven times more frequently in patients with this reduced awareness (Gold, Macleod, & Frier, 1994). Thus, despite the widespread use of injected insulin as the current standard-of-care for T1DM, as well as for many insulin-requiring patients with advanced type 2 diabetes mellitus (T2DM) and beta cell exhaustion, significant quality of life issues, co-morbidities, and an elevated risk of mortality remain challenges with the disease. Indeed, an enormous unmet need exists among millions of insulin-dependent diabetic patients.

As the primary pathogenesis of T1DM is loss of insulin-producing pancreatic beta cell mass, it is an ideal candidate for cell replacement therapy. Transplantation of cadaveric islets has proven to be an effective treatment for this high-risk patient population, resulting in insulin independence in the majority of treated patients. While cadaver islet transplant requires immunosuppression, which carries certain health risks, the therapy has demonstrated an appropriate risk-benefit ratio in these patients (CITR Coordinating Center, 2011).

Islet replacement can control blood glucose in a more biological and homeostatic manner than injectable pharmaceuticals, including the various forms of insulin currently on the market, thus reducing or eliminating the blood glucose excursion extremes that plague current therapy. In addition, by providing a more physiologic form of insulin (i.e., pro-insulin, as opposed to exogenous insulin injections), this treatment would also restore C-peptide, which has been reported to alleviate and/or prevent diabetic microvascular complications, such as neuropathy and nephropathy (Wahren, Kallas, & Simas, 2012). If found to be safe and effective, an islet

replacement product may prevent not only the short-term dangers of glycemic excursions, which can result in severe hypoglycemic events (SHE) and diabetic ketoacidosis, but also the long-term effects of the disease and current treatments. In addition, islet replacement therapy has the potential to vastly improve the quality of life for patients with T1DM.

While clinical proof-of-concept of the benefits of islet replacement has already been demonstrated through allogeneic islet transplantation (Barton, et al., 2012), one of the substantial limitations reported for cadaver islet transplant is a lack of suitable donor islets. Derivation of pancreatic lineage cells from human embryonic stem cells (hESC) has been a major focus of research as a means to produce islets for transplantation. Directed differentiation of hESC has the potential to result in a cell product that is predisposed to continue differentiation down the pancreatic lineage, and to mature into pancreatic endocrine hormone-producing cells, including glucose-responsive, insulin-producing cells, following implantation in vivo. Lastly, the islet transplantation field has long sought alternatives to the intra-portal transplantation site associated with cadaveric islet transplantation (Cantarelli & Piemonti, 2011).

1.2. Investigational Product

ViaCyte, Inc. is developing islet replacement therapies to treat diabetes, especially T1DM. A central focus of ViaCyte's overall strategy is utilization of a candidate somatic cell therapy comprised of pancreatic endoderm cells (PEC-01) differentiated from hESC that in nonclinical studies mature into pancreatic endocrine hormone-producing cells, including glucose-responsive, insulin-producing cells following subcutaneous implantation. The direct use of PEC-01 may provide an important alternative to the use of cadaver islets in T1DM subjects in which use of immunosuppression is justified. ViaCyte is developing a combination product for delivery of PEC-01 cells to the patient subcutaneously in the presence of immunosuppressive therapy as a potential treatment for high-risk patients with T1DM.

This product candidate, called VC-02 combination product (VC-02), is comprised of PEC-01 loaded in a Delivery Device (DD) with a membrane containing holes of controlled diameter and density designed to deliver and retain cells at the local implant site. The DD provides a means for maintaining the acute cell survival benefit provided by macroencapsulation while still permitting direct host vascularization of the graft. The holes will be large enough to allow capillary ingrowth, yet provide substantial retention of the cell product and thus facilitate formulation, delivery, and ultimate retrieval of the cells through explant of the combination product including the device and associated tissue capsule.

Delivery of PEC-01 in a fashion that permits direct vascularization of the graft is one of the primary intents of VC-02. ViaCyte has previously found that delivery of PEC-01 with direct vascular access permits robust efficacy in athymic nude rats whereas fully-encapsulated delivery (no holes) of PEC-01 fails to perform robustly. Nonclinical data in nude rats suggest that delivery of PEC-01 in this format may perform robustly as a result of (1) the direct vascularization of the implanted cells allowing for intimate transport of oxygen and nutrients and (2) a substantially reduced impact of the body's innate foreign body giant cell (FBGC) response. The formation of a layer of FBGC with cell processes that extend across a device membrane can impede transport of oxygen and nutrients leading to poor cell function and even cell death (Brauker, Shults, & Tapsak, 2004). Direct vascularization of the graft can overcome the negative impact of FBGC at the membrane

surface. Further, membrane openings enable ingress of other host cell types such as macrophages and other phagocytes that are capable of performing maintenance functions within the implanted cell tissue.

Subcutaneously, 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, direct 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. The insulin-producing capability of VC-02 increases gradually; in nonclinical studies, the product reaches glucose-responsive activity as early as three to four months after implantation, with maximal regulation of host glycemia occurring at approximately nine months.

Importantly, due to its stem cell-derived nature, VC-02 overcomes the limitations associated with use of deceased organ donors, which are principally: (1) severely limited supply of suitable cadaveric islets relative to the demand, and (2) patient risks associated with donated organs (e.g., donor-derived pathogens). Moreover, the delivery device, subcutaneous implantation route, and use of PEC-01 provide several advantages over current clinical islet transplantation, including:

- The ability to non-invasively monitor and image the graft site with conventional imaging modalities;
- A single, subcutaneous implantation procedure with the potential of delivering therapeutic benefit equivalent in duration and efficacy to islet transplants which in comparison often require multiple infusion procedures;
- Subsequent explant of the grafted device, allowing for biopsy and histological evaluation;
- Elimination of portal thrombotic events;
- Decreased risk of the deleterious effects on islets associated with instant blood mediated inflammatory reaction; and
- The potential for lower doses of required immunosuppressive drugs, thus decreasing the risk of adverse events, due to the hypo-immunogeneic nature of PEC-01 (Drukker, et al., 2006).

In summary, if the benefits of VC-02, as demonstrated in nonclinical studies, are realized in human trials, this product could deliver an essentially unlimited supply of robust and highly effective cells and could become a dramatically life-changing therapy for high-risk T1DM patients.

1.3. Nonclinical Information

In addition to the following sections, extensive nonclinical details on PEC-01, the DD, and VC-02 are available in the Investigator Brochure (IB).

1.3.1. Nonclinical 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 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 manufacture, raw materials have been subjected to a risk assessment and meet acceptance criteria for Phase 1 clinical manufacturing. To ensure sufficient safety of PEC-01, Good Manufacturing Practice (GMP) manufacturing of PEC-01 is 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.

It should be noted that the PEC-01 cells utilized in VC-02 represent the same drug substance tested extensively in nonclinical studies in support of the development of ViaCyte's VC-01 combination product.

1.3.2. Nonclinical Evaluation of Safety of the Delivery Device

Nonclinical evaluations of the Delivery Device component of VC-02 include a compilation of biocompatibility and integrity studies performed directly with the DD. Additionally, extensive studies were performed with ViaCyte's Encaptra® drug delivery system (EDDS), which is analogous in design and materials to the DD except that it does not have holes in the membrane of the device. Testing performed has demonstrated that the DD is capable of supporting survival, differentiation, and maturation of PEC-01 in vivo. Feasibility of utilizing the device to mitigate biodistribution of implanted cells has been demonstrated. Design verification activities confirmed the device membrane maintains its ability to retain PEC-01 within the intended area of implantation throughout the product life cycle, on assessing material stability, and on implementing complementary manufacturing quality controls to ensure all devices produced provide adequate safety performance. Completed studies confirm the device passes all biocompatibility tests. The DD is expected to significantly contribute to the safety profile of VC-02 by providing biocompatible and biostable retention of implanted cells.

1.3.3. Nonclinical Evaluation of Safety and Efficacy of VC-02

A total of [redacted] studies have been conducted with VC-02 to validate sufficient efficacy and safety in the nonclinical setting to enable first-in-human testing. The vast majority of rodents implanted in these murine studies were athymic nude rats, a model in which the FBGC response more closely mimics humans (relative to mice). Of these studies, [redacted] focused on the pharmacologic attributes of VC-02, resulting in the following observations:

- Homeostatic, glucose-stimulated insulin secretion is evidenced by C-peptide production at levels sufficient to protect against hyperglycemia yet not induce hypoglycemia.
- While different densities in the number of holes in a device result in similar efficacy, an optimal configuration protects implanted cells acutely after implantation while enabling host vascularization and ingress of host maintenance cells later in the engraftment process.

- The efficacy of VC-02 is not adversely affected by adjunct use of an immunosuppression drug regimen.
- Shelf-life stability (Section 5.1.3) for VC-02 was established, exhibiting robust efficacy post-implant when stored in cell medium for extended periods pre-implant.

Two studies were conducted with primary focus on establishing the safety profile of VC-02 in the nonclinical setting. One GLP study was completed to assess tolerability, systemic toxicity, tumorigenicity, and cellular distribution. The second study further assessed cellular distribution, but also the ability to explant all cells from the graft site through use of a luciferase-tagged PEC-01 cell line. Key findings were as follows:

- No indications of local implant site intolerability, systemic toxicity, cellular distribution beyond the intended implant location, or tumor formation were observed.
- Virtually all of the cellular content of the VC-02 graft is removed from the host upon VC-02 product explant (≥ 99.9%). Some limited PEC-01-derived cells can be found in host tissue surrounding the VC-02 implant, but they do not appear to migrate away from the implant site, instead remaining within the boundaries of the healed foreign body capsule.
- There is no evidence of systemic distribution of cells away from the implant site.

Additional details on the design and result of nonclinical studies are available in the VC-02 Investigator Brochure.

1.4. Potential Clinical Risks and Benefits

As this study is a first-in-human trial for VC-02, the clinical experience with this product is 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, the dosing requirement for exogenous insulin may decrease over time.

1.4.1. Potential Risks

Some of the potential risks for study participation are hypothetical at this stage of VC-02 development. There are safety-related, strictly-defined discontinuation and explant rules noted in Section 8.5. Potential risks include, but are not limited to the below items.

- There are inherent surgical risks with the implantation and explantation of VC-02 units including pain, bleeding, hematoma, seroma, tenderness, redness, scarring, and infection. Steps will be taken to minimize the risks and to make the subject comfortable during the procedure with anesthetic and post-procedure analgesia.
- With any implanted product, the possibility of migration or extrusion of the implant exists, along with the need for explantation.

- 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/or a burning sensation. Less likely side effects include nausea, vomiting, dizziness, drowsiness, 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 cords, 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 implant of VC-02, there may be an increased risk of HEs. Although the risk of HEs from grafted units is minimal based upon nonclinical results, as the implanted cells begin producing insulin, subjects and investigators need to monitor blood sugar levels closely and adjust the amount of required exogenous insulin.

In addition to Investigator review of glucose trends, insulin dosing, and HE occurrences, the Sponsor will conduct routine reviews of blood glucose data. These data are collected as part of the required study procedures. Subjects record insulin dosing and all HE occurrences on a study diary and glucometer data are electronically downloaded. The data are then available in near real-time for review. If potentially concerning trends are evidenced for an individual subject, the Sponsor will notify the Investigator and follow-up with the subject will occur if necessary (Section 7.10 – Blood Glucose Monitoring).

- There is a risk VC-02 will have a shorter than expected duration of efficacy or does not work as expected. [redacted] Cell viability and product function of VC-02 is expected to exceed the lifetime of animal models. The duration of exposure proposed for this clinical trial is up to two years.
- There is a risk of immune reactions and inflammatory responses due to the implantation of VC-02. The adjunct use of immunosuppressive drugs and anti-inflammatories, along with the design of the device, may minimize/eliminate this risk.
- The adjunct use of certain drugs may have side effects. The type(s) of medications used will be determined by the Investigator or Surgeon. Side effects may include, but are not limited to:
  - *Immunosuppressive Drugs:* Increased risk of infection, cancer, loss of appetite, nausea, vomiting, increased hair growth, and hand tremors.
  - *Anti-inflammatory Agents:* Stomach problems (e.g., pain, constipation, and diarrhea), kidney problems, anemia, dizziness, edema, abnormal liver tests, headaches, easy bruising, tinnitus, high blood pressure, and rash.

  - *High-dose Steroids*: Allergic reactions, changes in emotions or mood, changes in vision, eye pain, infection, edema, and high blood sugar levels.

- There are risks the implanted product may limit the subject's ability to be a candidate for future islet cell transplantation through sensitization.
- 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 the potential for VC-02 to rupture or break. [redacted] However, the device will not prevent penetration by sharp objects (e.g., insulin needle).
- 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. Potential Benefits

At this stage in VC-02 clinical development, there are no known benefits. However, there are several potential benefits of this therapy as noted below.

- Improved overall glycemic control
- Reduction in exogenous insulin dosing
- Reduction in the number of insulin injections and/or complete elimination of exogenous insulin injections
- Reduction in the frequency of blood glucose monitoring
- Reduction in the number of hypoglycemic events
- Improvement in hypoglycemia awareness (Leitao, et al., 2008)
- Reduction in the risk of micro- and macro-vascular complications
- Improvement in Quality of Life from an economic and lifestyle standpoint (e.g., decreased exogenous insulin requirements, fewer self-monitoring blood glucose supplies, dietary freedom)

The allowed number of VC-02 units implanted in Cohort 2 is higher than the allowed 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 subjects in Cohort 1 may experience some degree of clinical benefit as well.

2. OBJECTIVES AND ENDPOINTS

This first-in-human clinical trial will assess whether VC-02 can be implanted and maintained safely for up to two years in T1DM subjects with HU. During the first three to six months, VC-02 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.

2.1. Study Objectives

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

Cohort 1 Study Objectives:

- Assess the local and systemic safety and tolerability of VC-02 combination product when implanted into subjects with T1DM and HU.
- Assess histological proof of mechanism for VC-02 combination product (e.g., cell survival and differentiation to beta cells).

Cohort 2 Study Objectives:

- Evaluate the clinical efficacy and further assess safety and tolerability of VC-02 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.

Exploratory Objectives (Cohorts 1 & 2):

- Optimize the recommended surgical implantation procedure, anatomical location, and perioperative care for VC-02.
- Assess the effects of the host immune response to implanted VC-02 units.

2.2. Study Endpoint Measures

The study endpoints vary between the two cohorts and include safety, tolerability, and efficacy. Additionally, there are exploratory endpoints related to the surgical implantation procedure and anatomical locations of VC-02, perioperative care, host immune response, which includes both cohorts, as specified in Section 2.2.3.

2.2.1. Primary Endpoint Measures

Primary Endpoint / Cohort 1:

- Targeted safety and tolerability profile, inclusive of:
  - The incidence of AEs with causality related to VC-02 combination product, the surgical procedures required for VC-02 administration, and the immunosuppressive drug regimen.
  - The incidence of off-target growth as evidenced by implanted VC-02 units via lumen ultrasound measurements, or by histological examination of explants.
  - The incidence of immune sensitization defined by presence of donor anti-HLA antibodies absent prior to implant.

- Implant tolerability assessments (e.g., fever, erythema, pain, tenderness, induration) for up to four hours post-implantation and at subsequent visits.

Primary Endpoint / Cohort 2:

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

2.2.2. Secondary Endpoint Measures

Secondary Safety and Tolerability Endpoints: The comprehensive safety profile of VC-02 combination product implanted for up to two years as measured by:

- All reported AEs
- The incidence of immune sensitization defined by presence of donor anti-HLA antibodies absent prior to implant.
- Implant tolerability assessments (e.g., fever, erythema, pain, tenderness, induration) for up to four hours post-implantation and at subsequent visits.
- The incidence of subjects requiring a premature explant due to safety, tolerability, or malfunction issues.

Secondary Efficacy Endpoints:

- Change from baseline to Weeks 16, 26, 39, 52, 78, and 104 in C-peptide $AUC_{0\text{-}2h}$ or $AUC_{0\text{-}4h}$ following an MMTT;
- Time to onset of biological response of C-peptide following MMTT;
- Percent of subjects achieving a positive stimulated C-peptide (defined as >0.2 ng/mL) after implant;
- Change from baseline to Weeks 16, 26, 39, 52, 78, 104 in weekly frequency of hypoglycemic events;
- Percent of subjects free of severe hypoglycemic events from Week 16 to Weeks 20, 26, 39, 52, 78, and 104;
- Change from baseline to Weeks 16, 26, 39, 52, 78 and 104 in Clarke score;
- Change from baseline to Weeks 16, 26, 39, 52, 78, and 104 in average daily insulin dose in the seven days preceding the Clinic Visits;
- Percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose from baseline to Weeks 16, 20, 26, 39, 52, 78, and 104;
- Percent of subjects who achieve exogenous insulin independence; of those subjects achieving insulin independence, the percent achieving HbA1c <7.0%
- Percent of time spent with blood glucose values at various cut points (e.g., <54 mg/dL, ≥54 to <70 mg/dL, ≥70 mg/dL to ≤180 mg/dL, and >180 mg/dL) as measured by each subject's CGM device.

- Change from baseline to Weeks 16, 26, 39, 52, 78, and 104 in time-in-euglycemic range (≥70 mg/dL to ≤180 mg/dL), time-in-hypoglycemic ranges (<54 mg/dL and ≥54 to <70 mg/dL), and time-in-hyperglycemic ranges (>180 mg/dL) as measured by each subject's CGM

2.2.3. Exploratory Endpoint Measures

Exploratory Endpoints/ Cohort 1 and 2:

- Histological results of explanted units and any associated tissue capsule as evaluated for cell viability, vascularization, immune response, and/or cell maturation and differentiation.

3. STUDY DESIGN

This will be an open-label, FIH, clinical trial in subjects with T1DM and HU. Two cohorts are planned for enrollment in this trial, with enrollment of Cohort 1 occurring prior to enrollment of Cohort 2.

All enrolled subjects in Cohort 1 will have up to ten VC-02 units and in Cohort 2 will have up to eleven VC-02 units implanted [redacted] s 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].

At the end of the treatment period for each subject, all remaining implanted units will be removed, and the subject will be required to participate in a separate, follow-up, non-interventional, observational study. The primary purpose of this additional study is to ensure there are no long-term safety issues associated with previous implantation with VC-02.

Each Cohort is described in further detail below.

3.1. Cohort 1

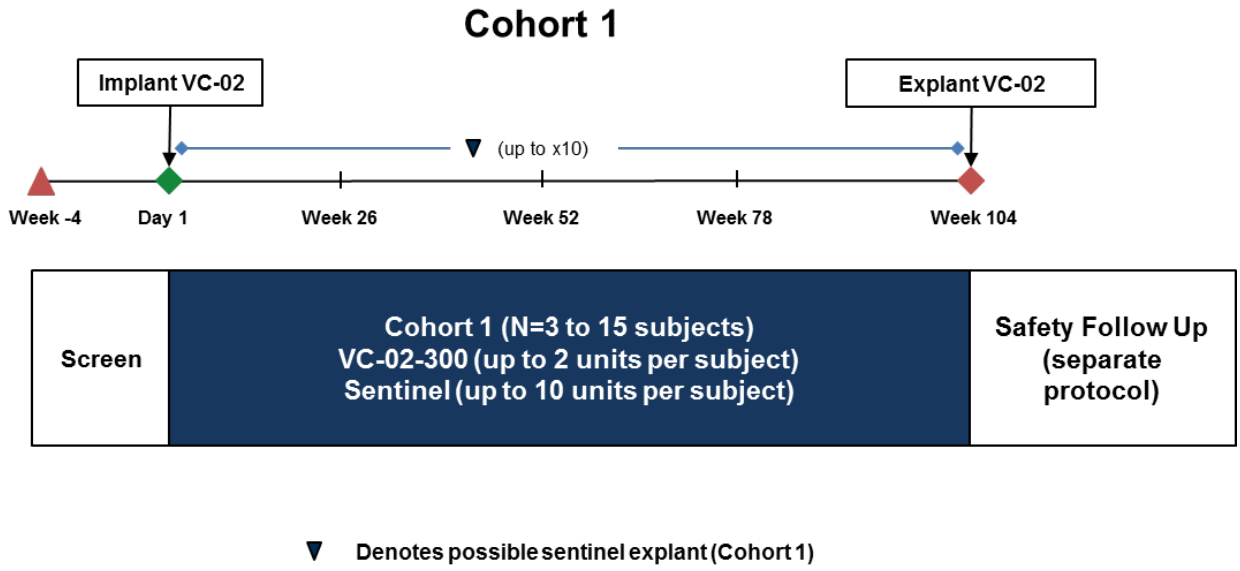
Enrollment of Cohort 1 will occur first in this study at one (1) or more clinical sites. A minimum of 3 and up to 15 subjects may be enrolled in Cohort 1. Initially, up to ten (10) VC-02-20 units (sentinels) will be implanted in Cohort 1 subjects in order to maximize the amount of available histologic data. However, the first three (3) subjects enrolled in Cohort 1 will not be implanted with VC-02-300 units. [redacted]. After the first three subjects are enrolled in Cohort 1, VC-02-300 units may then be implanted in subsequent subjects and the stimulated C-peptide levels will be monitored. These additional Cohort 1 subjects may be implanted with up to two (2) VC-02-300 units and up to six (6) VC-02 sentinels total. The decision as to the number of VC-02-300 units implanted in subsequent subjects will be data-driven and this number may be reduced. However, if no VC-02-300 units are implanted in these additional Cohort 1 subjects, up to ten (10) VC-02 sentinels may instead be implanted.

The total duration of treatment (implantation) may be up to two (2) years for each Cohort 1 subject. Sentinels may be explanted at various time points post-implant to assess the status of cell viability and differentiation, vascularization, and the host response. The VC-02-300 unit(s) and all remaining sentinel units will be explanted at Visit 17/Week 104. Including the requirements of the screening period, Cohort 1 subjects will complete a total of 18 study visits spanning approximately 25 months as outlined in Table 1 – Schedule of Assessments. At a minimum, the first three (3) subjects in Cohort 1 will be enrolled sequentially in order to assess safety and tolerability data thru Week 2 before implanting the next subject. For example, data thru Week 2 from the first subject will be formally reviewed by the Sponsor prior to allowing the Investigator to implant the next subject. If a treatment-related SAE is observed within the first two weeks in the subject, the implantation of the next subject will be postponed until consultation between the Sponsor and Investigator has devised appropriate safeguards. Overall, if no treatment-related SAEs are observed with the first three (3) subjects after each has reached Week 4, additional Cohort 1 enrollment may then be performed in parallel.

A target minimum of three (3) evaluable subjects will be enrolled as part of Cohort 1, but up to 15 total subjects may be enrolled in Cohort 1 if the Sponsor and/or Data Safety Monitoring Board (DSMB) determine that additional subject data are necessary to properly evaluate the investigational product and/or the implantation procedure. After the minimum of three (3) subjects have been enrolled in Cohort 1 and have completed thru Week 4, the Sponsor then has the ability to initiate enrollment of Cohort 2 and request the DSMB to meet to review the cumulative Cohort 1 data for safety, tolerability, and proof of mechanism.

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

Figure 1. Cohort 1 Study Schematic



3.2. Cohort 2

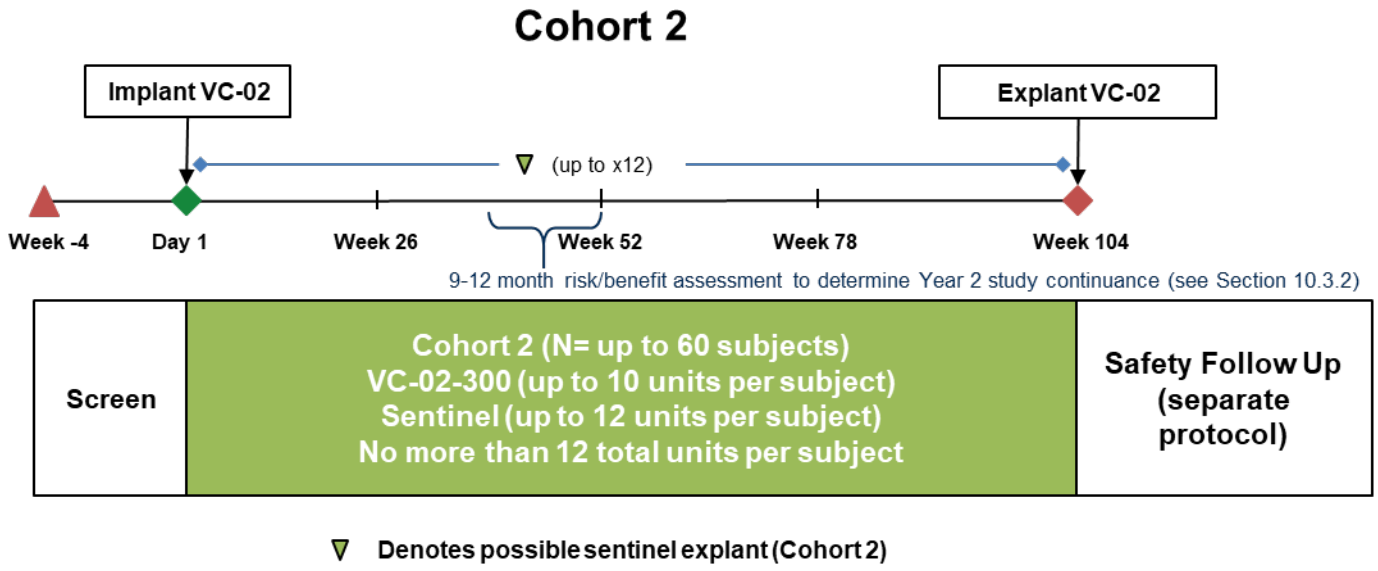
Enrollment of Cohort 2 will include up to 60 additional subjects who will be implanted with up to twelve (12) units. Of the twelve implanted units, no more than ten (10) will be VC-02-300 units, and the remainder will be VC-02-20 units. For example, if ten (10) VC-02-300 units are implanted, up to two (2) VC-02 sentinels may also be implanted.

Cohort 2 subjects will be implanted in cadres and will test a particular device configuration and/or implant strategy. Based on information obtained from subject explants within a given cadre, the need for an alternate device configuration and/or surgical implant technique (e.g., pharmacological intervention, implant site, etc.) may be identified in order to improve engraftment and cell survival outcomes. These changes will be implemented prior to the next cadre of subjects commencing implantation to drive VC-02 engraftment optimization.

Cohort 2 enrollment is competitive across approximately ten (10) sites, inclusive of those participating in Cohort 1. The total duration of treatment may be up to two (2) years for each Cohort 2 subject. Sentinels may also be explanted at various time points post-implant. All remaining VC-02-300 and sentinel units will be explanted at Visit 17/Week 104. Including the requirements of the screening period, Cohort 2 subjects will complete a total of up to 18 study visits spanning approximately 25 months as outlined in Table 1 – Schedule of Assessments.

The number of VC-02-300 units to be implanted in Cohort 2 subjects will be a data-driven decision and may vary between subjects. The Sponsor will review available C-peptide results from Cohort 1 subjects, as well as an ongoing review of C-peptide results from implanted Cohort 2 subjects, to determine the optimal number of VC-02-300 units to implant in subsequent subjects. The Sponsor generally intends to implant the least number of VC-02-300 units required to provide the intended therapeutic benefit. Pre-clinical data suggest [redacted] VC-02-300 units may provide enough therapeutic benefit to allow a subject to discontinue exogenous insulin; [redacted] units may be implanted in subjects, and the stimulated C-peptide levels will be monitored. However, if VC-02 does not function as robustly in humans as observed in pre-clinical models, then the number of VC-02-300 units may increase [redacted]

Figure 2. Cohort 2 Study Schematic



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

A minimum of three (3) and up to 15 subjects total will be enrolled in Cohort 1 at one (1) or more sites. Cohort 2 will enroll up to 60 subjects from approximately ten (10) sites. Therefore, the total enrollment possible for the trial (Cohort 1 and Cohort 2) is up to 75 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 criteria at the time of the screening period (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 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 the subject has been informed of all aspects of the trial.

2. Men and non-pregnant women 18-65 years of age.
3. Diagnosis of T1DM for a minimum of five (5) years.
4. Stable, optimized insulin 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. Insulin dosage at screening <1 unit/kg/day (using previous seven days as average).
6. The subject is an acceptable candidate for implantation and explantation of VC-02 as determined by the Surgeon and Investigator.
7. Willing to use the study-provided CGM system as instructed and to comply with system requirements during the trial.
8. 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.
9. Willing and able to comply with all scheduled visits, treatment plans, post-surgical care and restrictions, laboratory tests, fingerstick blood glucose monitoring, and other study procedures.
10. Documented hypoglycemia unawareness (Clarke score ≥4) or significant glycemic lability as assessed by the Investigator.
11. At least one severe hypoglycemic event, or for patients with CGMs, documentation of a low blood glucose value <54 mg/dL (<3.0 mmol/L), in the previous 12 months.
12. All male subjects and female subjects of childbearing potential must practice effective contraception during the study and be willing and able to continue contraception until final explant. For further details of contraceptive requirements for this study, please refer to Section 5.4.5.

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.

Diabetes-specific:

1. A detectable stimulated serum C-peptide at any time-point during the screening period, defined as >0.2 ng/mL (>0.0667 nmol/L).
2. Current use of any oral anti-diabetic medication.
3. Medical history of islet cell, kidney, and/or pancreas transplant.
4. Occurrence of six or more severe hypoglycemic events within six months of enrollment.
5. Known causes of diabetes other than T1DM.
6. Diabetic complications such as:
   a. Kidney disease (Stage 3 to 5),

b. Renal dysfunction (macroalbuminuria defined as protein of 2+ or greater on dipstick, MDRD eGFR <60 mL/min/1.73m^2)
c. Proliferative retinopathy (active or untreated)
d. Diabetic foot ulcers
e. Amputations attributable to diabetes
f. Severe peripheral neuropathy.

7. Hemoglobin A1C level of ≥10.0%.
8. Non-compliance with current anti-diabetic regimen.

Medical History:

9. 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.
10. Uncontrolled or untreated thyroid disease or adrenal insufficiency.
11. Active alcohol abuse or history of alcohol abuse within five (5) years of enrollment.
12. Positive urine drug screen for substances of abuse during the screening period or history of drug abuse within five (5) years of enrollment. Medical marijuana use may be allowed by the PI after consultation with the Medical Monitor and/or Sponsor.
13. 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.
14. Known allergies to portions of the cellular excipients used as cell preservation solution or the PEC-01 manufacturing process (i.e., bovine, porcine allergies).
15. History of severe asthma or COPD.
16. BMI ≥32 kg/m^2 or <18 kg/m^2 at screening.
17. 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.
18. Active infection or known history of Hepatitis B or C.
19. Positive serology for HIV at screening.
20. Evidence of previous tuberculosis infection (including BCG vaccination or positive PPD).
21. Negative serostatus for Epstein-Barr virus.
22. 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.

23. Sustained hypertension defined as average systolic ≥160 mmHg or diastolic ≥90 mmHg at screening.

24. 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.

25. 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.

26. History of coagulopathy.

27. Any other medical condition, for which in the opinion of the Investigator, the subject is not suitable for the trial. Examples may include clinically significant medical and non-medical conditions, and/or psychiatric disorders.

Exclusionary Procedures or Medications

28. Participation in another 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.

29. Planned surgery in the general location of the implanted units [redacted] at any time during study participation.

5. INVESTIGATIONAL PRODUCT & STUDY INTERVENTIONS

5.1. VC-02™ Combination Product Description

VC-02 Combination Product is comprised of two distinct components: (1) PEC-01 pancreatic endoderm cells derived from hESC and (2) a durable, removable, Delivery Device (DD) designed to deliver and retain cells at the local implant site. During the first three (3) to six (6) months following implantation, the VC-02 units are expected to vascularize adequately, and the PEC-01 cells are expected to differentiate into mature glucose-responsive, insulin-producing cells, capable of secreting insulin in response to serum glucose concentration. VC-02 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.

[redacted]

[redacted]

Extensive additional details about the product and its two components (PEC-01 and the DD) are available in the VC-02 IB.

5.1.1. Manufacturing, Formulation, Packaging, and Labeling

[redacted]

5.1.2. Transport of Investigational Product to Site

ViaCyte ships investigational product to the site where the Surgeon performs the implantation. Units are appropriately labeled, with each shipper containing implants intended for a designated patient. Up to [redacted] can be shipped together in a single environmental shipper. The insulated, shipping container maintains the target temperature range of the product for the duration of the shelf-life. After implantation, the environmental shipper(s) and temperature logger(s) shall be returned to ViaCyte or designee. Additional details will be provided in the study reference manual.

5.1.3. Product Storage, Stability, and Accountability

The shelf-life of the product is qualified f[redacted] The "Use By Date" is present on each unit.

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

[redacted] 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 its designee may wish to retrieve the damaged product and/or shipping container so an appropriate evaluation can be done.

The Investigator is responsible for the accountability of all used and unused study supplies. Unused or partially used supplies must be returned or destroyed, and accounted for as directed in a study reference manual.

5.1.4. Dosage and Administration

All properly consented subjects will receive a unique, study subject ID number. Those subjects meeting eligibility criteria are enrolled at Visit 3/Day 1 and implanted with VC-02. As this is an open-label study, the subject, Sponsor, and Investigator are not blinded and will know how many and which types of VC-02 are implanted depending on the cohort the subject enrolls into:

- In Cohort 1, subjects are implanted with up to two (2) VC-02-300 units and up to six (6) sentinels; or up to ten (10) sentinels only.
- In Cohort 2, subjects are implanted with up to twelve (12) units. Of these, no more than ten (10) may be the VC-02-300 units, with the remainder being sentinel units.

During Cohort 2, as alternate device configurations, surgical implant techniques, and/or pharmacological interventions are implemented in order to improve engraftment outcomes, a subset of patients may be implanted with "control" sentinels. These VC-02-20 control sentinels are identical to the VC-02-20 sentinel with respect to materials and manufacturing process, except that the VC-02-20 control sentinel will not contain holes. The control sentinel is being evaluated for research purposes only. For the alternate strategies implemented during Cohort 2, the control sentinel will enable ViaCyte to determine the effect on PEC-01 survivability, engraftment, and functionality in a non-perforated delivery device.

After consultation with the Investigator and/or Surgeon, the Sponsor will determine the overall implantation and explantation strategy for a subject, including the total number of VC-02-300 and sentinel units to be implanted, the anatomical locations of the implants, the immunosuppressive regimen, any additional adjunct medications or treatments, and the schedule of explant procedures. All implant and explant procedures will be executed under an anesthetic with or without sedation at the discretion of the Surgeon. Documentation of the implant and explant plans for a subject will be provided by the Sponsor to the Investigator.

VC-02-300 units are the dosage formulation intended to provide a measurable, therapeutic benefit to enrolled subjects. However, VC-02-20 units contain [redacted]. It is anticipated that approximately 200,000 IEQ, equivalent to approximately 20% of normal beta cell mass, are required to achieve insulin independence. Assuming the data from Cohort 1 and early

subjects enrolled in Cohort 2 support a dose increase, some subjects in Cohort 2 may be implanted [redacted]

Table 2. VC-02 Dosing Projections (75 kg Human)

Device Type and (Quantity)	At Implant (Cell Input)			4 Months (Cell Output)		9 Months (Cell Output)	
	PEC-01 cells ($x10^7$)	PEC-01 cells (10^6/kg)	Fold Safety Factor	IEQ	Per Kilogram IEQ	IEQ	Per Kilogram IEQ
VC-02-20 (6)	[redacted]						
VC-02-20 (10)	[redacted]						
VC-02-20 (12)	[redacted]						
VC-02-300 (1)	[redacted]						
VC-02-300 (10)	[redacted]						

* If more than one VC-02-300 unit is required due to lower levels of achieved clinical efficacy, the delivered numbers of total PEC-01 cells and PEC-01 cells per kg (cell input) increase commensurately, but the maximum target output (IEQ and IEQ / kg) would remain constant and/or within homeostasis.

The administration of the investigational product is performed via implantation on Visit 3 (Day 1). The preparation and implantation procedures involve step-by-step instructions which are detailed in Section 7.4 and the IFU. Site personnel will be trained to ensure compliance with the product handling and implantation procedures.

Due to the nature of the product under investigation, "dose" adjustments (e.g., an increase or decrease) of the implanted VC-02 are not permitted. However, at the discretion of the Sponsor and after consultation with the Investigator, or if a unit is suspected of malfunctioning or being damaged (Section 13.6), explantation of one VC-02-300 unit is allowed at any time post-implant for a subject without needing to withdraw the subject from the study. 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-02-300 units and all remaining sentinels explanted.

As VC-02 is implanted into each subject, assessment of subject compliance with the investigational product does not apply. If, however, the expected number of sentinels or VC-02-300 units is not implanted into a subject, this needs to be recorded in the subject's source documentation.

5.2. Immunosuppression Medications

An immunosuppressive regimen will be prescribed for each subject to facilitate the engraftment and long-term function of implanted VC-02 units. The overall regimen may include the following agents (**Day 1 is Implant Day*):

- Induction (Cohort 1)
  - Basiliximab: Recommended course of 20 mg IV on Day 1 and Day 5. However, it may be administered as early as Visit 2 (Week -4).
- Induction (Cohort 2)

  If data collected from Cohort 1 indicate sufficient engraftment and cell viability is achieved with basiliximab, its use will continue in Cohort 2. However, if data from Cohort 1 and/or data collected in subsequent subjects in Cohort 2 indicate insufficient cell viability is achieved, the following agent may be utilized:
  - Anti-thymocyte globulin (ATG) recommended course:
    - Day -2 (0.5 mg/kg IV) – required dose
    - Day -1 (1.0 mg/kg IV) – required dose
    - Day 1 (1.5 mg/kg IV) – required dose
    - Up to two additional 1.5 mg/kg/day IV doses of ATG may be administered (on Day 2, and/or Day 3). Prior to any additional dose administration of ATG, an absolute lymphocyte count (ALC) will be obtained locally. If the ALC has been reduced by at least 90% versus the pre-ATG administration level, additional dose(s) of ATG may not be required. The Investigator should contact the Sponsor to determine the need for additional dosing.

    However, ATG may be administered using the above dosing schedule as early as Visit 2 (Week -4).
- Maintenance (both Cohorts)

  The starting doses and target serum trough concentration levels listed below are recommendations. As determined by the Investigator and after consultation with the Sponsor, the doses and target trough levels may be adjusted.
  - Mycophenolate mofetil (MMF): Recommended starting dose of 1 gm PO BID as early as Visit 2 (Week -4). Adjust the dose downward for gastrointestinal side effects. Mycophenolic acid (Myfortic) may be taken alternatively to alleviate such side effects. Trough level measurements for MMF are not required.
  - Tacrolimus:

- If combined with MMF: Recommended starting dose of 2 mg PO BID as early as Visit 2 (Week -4); target serum trough concentration level of 10-12 ng/mL during the first three (3) months. Adjust the dose to maintain a serum trough concentration level of 7-9 ng/mL thereafter. Serum creatinine values should also be collected in conjunction with Tacrolimus trough levels in order to monitor for potential renal toxicity.
- If combined with sirolimus and MMF: Recommended starting dose of 0.1 mg/kg per day in two (2) equal divided doses to achieve a target serum concentration of 6-8 ng/mL.

  - Sirolimus: Recommended starting dose of 0.1 mg/kg/day as early as Visit 2 (Week -4); target serum trough concentration level of 8-10 ng/mL by at least Week -2 prior to implantation. Post-implant, target serum trough concentration levels of 12-15 ng/mL for the three (3) months after implantation and serum trough concentration levels of 10-12 ng/mL thereafter plus MMF (2 g/day).

- Anti-inflammatory (both Cohorts)
  - Etanercept recommended course:
    - Day 1 (50 mg IV*)
    - Day 4, Day 8, and Day 11 (25 mg SC)

    **Subcutaneous administration if required per local labeling*.
  - Steroids (e.g., prednisone): Recommended short-term course of steroids (e.g., approximately one-month post-implant) with a controlled taper. The overall dosing and taper period will be determined by the Investigator after consultation with the Sponsor. During the use of steroids, the Investigator should manage fluctuations in blood glucose levels in accordance with local standard of care as needed.

Additional medications can be prescribed by the Investigator to increase the safety and efficacy potential of the product after consultation with the Sponsor. As determined by the Investigator, medications and/or doses may be adjusted for safety reasons. The Investigator should refer to the applicable product labeling and package insert for details on the known and potential risks associated with the use of the immunosuppressive medications prescribed as adjunct treatment for each subject. As needed, the dosages of these medications should be adjusted to achieve the target blood concentrations (Section 7.11.3) and to minimize the potential for adverse events.

As additional data are gathered in this trial, changes in the required immunosuppressive regimen may be necessary to enhance safety and/or efficacy of VC-02. The Sponsor will notify the sites and Ethics Committee (if necessary) of such changes as information becomes available.

5.3. Other Concomitant Medications and Treatments

The Surgeon or Investigator, in consultation with the Sponsor, may prescribe additional concomitant medication or treatments [redacted]

[redacted]

Therapies for pre-existing and new medical conditions will be provided per local standard of care at the discretion of the Investigator. Any pre- and post-procedure drug regimens (e.g., sedatives, anesthetics, and pain relievers) will also be given per standard of care as determined by the Investigator or Surgeon.

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-02. The Sponsor will notify the sites and Ethics Committee (if necessary) of such changes as information becomes available.

For details related to use of exogenous insulin, refer to Section 5.4.2.

5.4. Lifestyle Guidelines

Subjects will be instructed concerning the Lifestyle Guidelines described below at the times indicated in the Schedule of Assessments Table 1. Sites should remind subjects of these restrictions several days prior to visits and reinforce at all visits throughout the trial to avoid adversely impacting study procedures.

5.4.1. Dietary Restrictions

Subjects must abstain from all food and drink (except water) at least 8 hours prior to any blood sample collection for clinical lab tests unless otherwise indicated.

Subjects not fasting before a scheduled clinic visit will be required to return in a fasted state to complete lab sample collection within the protocol visit window. Any assessments not requiring the subject to be fasting can be performed at the originally scheduled clinic visit.

Subjects will be counseled on appropriate dietary and lifestyle guidelines in accordance with local standards of care for T1DM beginning at Day 1 (Visit 3) and expected to follow the advice throughout participation of the trial.

5.4.2. 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 insulin may be modified over the course of the study. However, the types and brands of insulin used by the subject should remain consistent as much as possible. Also, the insulin delivery method for a subject (e.g., pump or multiple daily injections) should not change without consulting the Sponsor and/or Medical Monitor. Subjects are required to log their insulin doses every day on the study diary throughout participation in the trial (Section 7.10.1).

Post-implant, subjects cannot inject insulin in areas near implantation sites. Additionally, while wearing the CGM sensor, subjects cannot inject insulin within three (3) inches of the sensor.

5.4.3. Physical Activity

For a week post-implant, subjects must limit significant physical activity 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-implant, 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., weight training and long-distance running) within 48 hours before each lab sample collection. Moderate activities such as low-distance running, aerobics, bicycling, or swimming, may be acceptable.

5.4.4. Alcohol, Caffeine and Tobacco

As part of standard management of diabetes, the intake of alcohol should be limited.

Caffeine and nicotine products are prohibited for at least 30 minutes prior to ECG and vital sign determinations.

5.4.5. Contraception

All female subjects and male subjects (who in conjunction with a female partner, as applicable) 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 while VC-02 is implanted. The subject will select the most appropriate method(s) of contraception from the list below. The Investigator will instruct the subject on consistent and proper use, and at each study visit, will confirm and document consistent and proper use. In addition, the Investigator will instruct the subject to contact the site immediately if the 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) with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; vasectomy; or intrauterine device (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).

5.4.5.1. Women of Non-childbearing Potential

Women of non-childbearing potential will be allowed into the study and will not need to follow contraception requirements outlined in Section 5.4.5. To be considered of 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 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 -5).

5.4.6. Other Restrictions

Subjects should not undergo magnetic resonance imaging (MRI), computed tomography (CT), or diathermy treatment while wearing the CGM sensor. The CGM transmitter and sensor should be removed because of the magnetic fields and heat used in these procedures.

As additional data are gathered in this trial, there may be other restrictions implemented. These restrictions could be related to the efficacy or safety of VC-02. If required for safety reporting, the information will be communicated to sites as quickly as possible in order to inform the subjects and/or Ethics Committee.

6. STUDY SCHEDULE

The clinic visit schedule for subjects is outlined in Table 1 – Schedule of Assessments. With documented sponsor permission, on a case-by-case basis, certain protocol-required assessments may be performed remotely.

To minimize variability in data, sites should attempt to schedule visits on the same day of the week and same time of day for a subject throughout the trial. When multiple procedures occur at a visit, the following order of procedures should be adhered to as much as possible:

1. 12-lead ECG
2. Vital signs (sitting blood pressure, pulse, and temperature)
3. Blood and urine samples
4. Mixed Meal Tolerance Test (MMTT) or Simplified Oral Glucose Challenge Test (SOGCT). For visits requiring both an MMTT *and* an explant procedure, the site may perform the MMTT within five (days) prior to the explant procedure.
5. Location ultrasounds: May be performed up to three (3) days prior to an explant.
6. Implant or explant procedures
7. Other procedures: May be obtained in any order either prior to blood samples or after, but not sooner than ECG or vitals.

Cohort 1 and Cohort 2 subjects follow the same schedule of assessments (Table 1). A difference in the number of sentinels implanted and explanted may occur, but all other scheduled procedures remain consistent between Cohort 1 and Cohort 2.

6.1. Visit 1 / Screening (Week -5 to Week -4)

It is permissible for this visit to occur over multiple days. Subjects must be fasted prior to this visit. The following procedures are completed:

- Obtain informed consent.
- Obtain a 12-lead ECG.
- Obtain vitals.
- Measure height and weight
- Collect demography, medical history (including smoking status, alcohol frequency, and hormonal status, as well as prior (within 30 days) and concomitant medications.
- Obtain contact information of the subject's health care provider and family members in order to reach subject if other contact methods are unsuccessful.
- Perform a complete physical exam (PE).
- Administer the Clarke Survey.
- Obtain all laboratory samples per the Schedule of Assessments; dispense home collection supplies for the baseline urine albumin/creatinine sample.
- Perform urine pregnancy test using the study-provided kit.
- Conduct the SOGCT.
- Review eligibility criteria to assess suitability for the trial.
- Review Lifestyle Guidelines.
- Contact the Sponsor to schedule provisioning of VC-02 for an implant date.

6.2. Visit 2 / Screening (Week -4 to Week -2)

Subjects meeting eligibility criteria will return for Screening Visit 2 (Week -4). Subjects must be fasted for this visit. The following procedures will be completed:

- Review and confirm continued eligibility criteria.
- Obtain weight/vitals.
- Obtain all laboratory samples per the Schedule of Assessments.

  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 7.11.4).
- Perform the 4-hour MMTT. This is the baseline MMTT for efficacy evaluations.

- Dispense Continuous Glucose Monitoring (CGM) equipment and provide instructions. Insert the first sensor at the clinic. Confirm the CGM is functioning prior to the subject leaving the clinic.
- Dispense Self-Monitoring Blood Glucose (SMBG) equipment and provide instructions. Use of the meter provided by the Sponsor is required.
- Dispense the study diary and provide instructions. This is where the subject will capture insulin doses, details on HEs, and SMBG values. **Remind the subject that eligibility for the trial requires daily compliance with entries between Visit 2 and 3.**
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.
- Contact the Sponsor to report any schedule changes or updates to the implant date.

The expected duration of the Screening Period is up to approximately five weeks. If the Enrollment Visit 3 is scheduled to occur beyond six weeks (>42 days) from the occurrence of Screening Visit 1, sites must contact the Sponsor before proceeding. Depending on the expected duration of the delay in conducting Visit 3, an Unscheduled Visit may be required to repeat certain screening procedures.

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

6.3. Visit 3 / Enrollment and Implantation (Day 1)

Subjects must be fasted for this visit. The following procedures will be completed:

- Ensure eligibility criteria continue to be met.
- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Perform urine pregnancy test using the study-provided kit. Results must be available before the implant procedure commences.
- Collect and review CGM, SMBG, and diary data and verify subject has demonstrated compliance with diary entries; dispense additional supplies.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and Concomitant Medications.
- Prepare subject for implantation.
- Implant VC-02-300 and sentinel units.
- Obtain video and/or photos of the implantation procedure (if requested by Sponsor).
- Dress the subject with the appropriate compression garments.

- Assess subject for up to four hours post-implantation for AEs.
- Remind subject to limit significant physical activity to ensure optimal healing at implantation sites. Instruct the subject on the proper use of all post-implant treatments.

6.4. Visit 4 (Day 2)

There is a +1-day window for this visit. Subjects do *not* need to fast for this visit. The following procedures will be completed:

- Perform a targeted PE focusing on the implantation site(s).
- Obtain weight/vitals.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.

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

- Perform ultrasound to locate the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).

6.5. Visit 5 (Week 2)

There is a ±2-day window for this visit. Subjects must be fasted for this visit. The following procedures will be completed:

- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain laboratory samples per the Schedule of Assessments.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.

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

- Perform ultrasound to locate the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).

6.6. Visit 6 (Week 4)

There is a ±3-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 laboratory samples per the Schedule of Assessments.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.

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

- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).

6.7. Visit 7 (Week 8)

There is a ±7-day window for this visit. Subjects must be fasted for 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. Provide counseling and assistance to subject if there are compliance issues.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.
- Perform the *safety* ultrasound assessment of implantation sites.
- Conduct the 2-hour MMTT.

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

- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).

6.8. Visit 8 (Week 12)

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

- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain all laboratory samples per the Schedule of Assessments.

- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.
- Conduct the 2-hour MMTT.

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

- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).

6.9. Visit 9 (Week 16)

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

- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Administer the Clarke Survey.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.
- Perform the *safety* ultrasound assessment of implantation sites.
- Conduct the 2-hour MMTT.

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

- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).

6.10. Visit 10 (Week 20)

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

- Obtain weight/vitals.

- Obtain all laboratory samples per the Schedule of Assessments. Dispense home collection supplies for the urine albumin/creatinine sample.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.
- Conduct the 2-hour MMTT.

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

- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).

6.11. Visits 11 and 13 (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. The following procedures will be completed:

- Obtain 12-lead ECG.
- Obtain weight/vitals.
- Perform a complete PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Perform urine pregnancy test using the study-provided kit (Week 52 only).
- Administer the Clarke Survey.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Perform the *safety* ultrasound assessment of implantation sites.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.
- Perform the 4-hour MMTT.

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

- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).

6.12. Visit 12 (Week 39)

There is a ±14-day window for this visit. Subjects must be fasted for these visits. The following procedures will be completed:

- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Dispense home collection supplies for the urine albumin/creatinine sample.
- Administer the Clarke Survey.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.
- Conduct the 2-hour MMTT.

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

- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).

6.13. Visits 14 and 16 (Weeks 65 and 91)

There is a ±14-day window for these visits. Subjects must be fasted for this visit. The following procedures will be completed:

- Obtain weight/vitals.
- Obtain all laboratory samples per the Schedule of Assessments. Dispense home collection supplies for the urine albumin/creatinine sample.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.
- Conduct the 2-hour MMTT.

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

- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor)

6.14. Visit 15 (Week 78)

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

- Obtain weight/vitals.
- Perform an abbreviated PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Administer the Clarke Survey.
- Collect and review CGM, SMBG, and diary data; dispense additional supplies. Provide counseling and assistance to subject if there are compliance issues.
- Perform the *safety* ultrasound assessment of implantation sites.
- Dispense immunosuppression drugs and provide instructions for dosing (as needed).
- Assess AEs and concomitant medications.
- Conduct the 4-hour MMTT.

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

- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Explant unit(s).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor)

6.15. Visit 17 / Study Completion (Week 104) or Early Termination

There is a ±7-day window for this visit. Subjects must be fasted for this visit.

If a subject withdraws or is discontinued from the study at any time, the procedures outlined in Visit 18 should be performed and the subject will be followed in the long-term, follow-up study (VC02-201). The following procedures will be completed:

- Obtain 12-lead ECG.
- Obtain weight/vitals.
- Perform a complete PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Perform urine pregnancy test using the study-provided kit. Pregnancy test should occur on the same day as the final explantation procedure.
- Collect all necessary study-related equipment.
- Administer the Clarke Survey.
- Review CGM, SMBG, and diary data.

- Dispense immunosuppression drugs and provide instructions for taper dosing (as needed).
- Assess AEs and concomitant medications.
- Perform the 4-hour MMTT.
- Perform the *safety* ultrasound assessment of implantation sites.
- Perform ultrasound to *locate* the unit(s) planned for explantation (up to 3 days prior).
- Prepare subject for explantation procedure:
  - Explant all remaining VC-02-300 and sentinel units (if applicable).
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).
- Review participation requirements for the long-term, follow-up study (ICD process for Protocol VC02-201 [safety-follow-up study] follow-up study can be initiated).
- Remind subject of the follow-up Visit 18.

6.16. Follow-up Visit 18 (Week 105)

There is a ±3-day window for this visit. All subjects, regardless of whether or not they completed the trial, complete this visit to follow-up on unresolved AEs and the post-explantation experience. The following procedures will be completed:

- Obtain weight/vitals.
- Perform a targeted PE of explantation site(s).
- Assess AEs and concomitant medications.
- Obtain photos of the explantation sites (if requested by Sponsor).

6.17. Unplanned or Unscheduled 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:

- Laboratory testing to evaluate immunosuppression drug levels.
- 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.
- Repeat or follow-up ultrasound evaluations (safety or location).

- Explant of a VC-02-300 unit or sentinel unit.
- Perform an SOGCT or MMTT.
- Obtain video and/or photos of an explantation procedure.
- Administration of immunosuppression drugs

Source documentation should reflect the occurrence of all Unplanned Visits. Data may be collected from these visits depending on the procedures conducted. A subject may need to be in a fasted state for Unplanned Visits depending on the laboratory tests required. (e.g., lipid panel or MMTT).

7. STUDY ASSESSMENTS

Every effort should be made to ensure protocol-required tests and procedures are completed as described. Rarely, circumstances outside the control of the Investigator 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 will document the reason along with corrective and preventive actions taken to ensure normal processes are adhered to as soon as possible.

In addition to the protocol-required assessments, the Investigator may conduct additional tests or procedures to ensure the safety and well-being of a subject in accordance with local standards of care. Source documentation should reflect the occurrence of these additional procedures.

7.1. Clinical Evaluations

7.1.1. Physical Examination

There are three types of PEs performed over the course of the study: complete, abbreviated, and targeted. All PEs must be performed by the Investigator or qualified designee. It is preferred that the same person conduct the same-type of PE for each subject over the course of the study Other body systems should be evaluated as per the judgment of the Investigator as needed to evaluate AEs.

Details of each are described below.

- A **complete** PE is performed at screening Visit 1 (Week -5), Visit 11 (Week 26), Visit 13 (Week 52) and Visit 17 (Completion / Early Termination). Body systems evaluated 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 source documents and any significant findings on the screening PE must be recorded on the Medical History CRF. All abnormal, clinically significant changes from the screening PE must be captured as AEs.
- An **abbreviated** PE is performed at Visit 3 (Day 1), Visit 5 (Week 2), Visit 6 (Week 4), Visit 8 (Week 12), Visit 12 (Week 39) and Visit 15 (Week 78). The abbreviated exam assesses the heart, lungs, abdomen, extremities, and skin (including implantation and/or explantation site[s]).

- A **targeted** PE focuses on the evaluation of the healing status at the implantation and/or explantation sites. Targeted PEs are performed at Visit 4 (Day 2) and Visit 18 (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.

7.1.2. Body Weight

Subjects are weighed at every visit on the site's designated, calibrated scale throughout the study. Preferably, weight is taken at approximately the same time of day, after voiding, and while wearing a gown or light clothing (no shoes or socks). Weight is reported in either pounds or kilograms.

7.1.3. 12-lead ECG

A single, supine 12-lead ECG is obtained on the site's equipment at the visits noted in the Schedule of Assessments. ECGs should be performed after the subject has rested for at least 10 minutes in a supine position and prior to vital signs and blood collection. The screening ECG is the baseline ECG for the study. All ECGs collected during the trial (planned and unplanned) should be reviewed at the site for safety monitoring. The Investigator is responsible for retaining copies of the ECG reports.

All abnormal, significant findings on the screening ECG must be recorded on the Medical History CRF. Over the course of the study, any abnormal, 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 (BP), pulse rate, and temperature. BP and pulse rate should be measured using the site's equipment. The following method should be used to record sitting BP and pulse rate for subjects.

- Subjects will refrain from nicotine products and/or caffeine at least 30 minutes prior to 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.
- Readings should be done on the same arm at each visit, preferably the non-dominant arm.
- Measurement should begin after at least five minutes of rest.
- Assessment of pulse rate can be manual or automated. 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 blood pressure and pulse rate measurements.

7.2. Mixed Meal Tolerance Test (MMTT)

MMTTs are conducted after all other vital signs evaluations and laboratory tests have been collected. The MMTT test should only be started if the subject has been fasting for at least eight

(8) hours. 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 to begin the MMTT. If the fasting glucose is not initially within range, the site may recheck levels while the subject is still at the clinic. If the fasting glucose remains outside of the allowed range, the subject must return to the site within the visit window and attempt the MMTT again.

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 occur at least 30 minutes prior to any blood collections on the days MMTTs are performed. The subject should sit upright during the test. Slow walking is permitted, but vigorous exercise should be avoided.

Baseline, fasting blood samples are drawn for glucose and C-peptide within approximately five minutes prior to the start of the meal test. At time = 0, the subject drinks Boost® Hi-Protein (volume equal to 6 mL/kg body weight to a maximum of 360 mL). The entire drink must be ingested within 15 minutes.

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. Further details regarding MMTTs may be outlined in the study reference manual.

7.2.1. 4-Hour Mixed Meal Tolerance Test

The 4-hour MMTT is conducted during Visit 2 (Week -4), Visit 11 (Week 26), Visit 13 (Week 52), Visit 15 (Week 78), and Visit 17 (Completion or ET). In addition to the time = 0 collection, samples for glucose and C-peptide are also collected at 30, 60, 90, 120, 180, and 240 minutes after the start of the Boost® meal test.

7.2.2. 2-Hour Mixed Meal Tolerance Test

The 2-hour MMTT is conducted during Visit 7 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 12 (Week 39), and Visit 14 (Week 65), and Visit 16 (Week 91). In addition to the time = 0 collection, samples for glucose and C-peptide are also collected at 30, 60, 90, and 120 minutes after the start of the Boost® meal test.

7.3. Simplified Oral Glucose Challenge Test (SOGCT)

All subjects complete the SOGCT at Visit 1 to confirm a stimulated C-peptide level >0.2 ng/mL is not presented (per the exclusion eligibility criterion). After all other required fasting blood and urine samples for the visit have been collected, a fasting C-peptide sample is collected and at time = 0 the subject then drinks Boost® Hi-Protein (volume equal to 6 mL/kg body weight to a maximum of 360 mL). The entire drink must be ingested within 15 minutes. The second C-peptide sample is then collected at any time between 30 to 60 minutes after the start of the SOGCT.

7.4. Implantation Procedure

Implantation occurs at Visit 3 (Day 1). The number of VC-02-300 and sentinel units implanted can vary and depends on whether the subject has been enrolled in Cohort 1 or Cohort 2

(Sections 3.1 and 3.2). All units are implanted [redacted]

A detailed description of the implantation procedure and surgical technique will be provided in the VC-02 IFU and as part of site training. Site personnel are required to complete training on the procedure and handling of VC-02 prior to conducting an implantation. As much as possible, all implant procedures performed for subjects at one site should be conducted by the same Surgeon. [redacted]

Details of the surgical procedure and location of each implanted unit will be collected on source documents 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 (e.g., placement of implanted units, number of incisions, dissection technique). As this is a FIH study, there is the possibility the implantation procedures will be modified based on data collected. To support the safety, tolerability, and efficacy profile of VC-02, updates and additional training on the surgical procedures may occur as needed during the study.

7.4.1. Post-Implant Discharge Instructions and Assessments

Immediately following the implant procedure, the subject will remain in the clinic for up to four hours following the procedure to monitor for AEs. Clinical monitoring will be performed to identify and assess: bleeding, bruising, redness, localized swelling, pain (discomfort), and any other clinical significant conditions.

Additionally, subjects will be monitored for potential immunological reactions to the implantation by traditional symptoms and signs including: anaphylaxis, acute breathing problems, 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. Occurrence of any of

these events will be captured as AEs. If the Investigator suspects the subject may be having an immunological reaction, the Sponsor must be contacted immediately.

Thereafter, either release or extended observation of the subject is at the discretion of the Surgeon and/or Investigator. Upon discharge, the subject should be provided instructions regarding the required Lifestyle Guidelines (Section 5.4), proper wound care and evaluation, and any prescribed concomitant therapies and/or treatments required to facilitate the implantation healing and engraftment process (Sections 5.2 and 5.3). For the week following the implantation, subjects are advised to limit significant physical activity to ensure optimal healing.

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.

7.5. Photographs of Implantation and Explantation Sites

Photographic images of subjects may be obtained during the study to visually document the anatomical implantation and explantation sites. The Sponsor will notify the Investigator when photographs are requested and provide instructions for capturing the appropriate images. To maintain subject confidentiality, images will be limited to the implantation and explantation sites and will not include images of the subject's facial features or any other uniquely identifiable physical features. If such features are unintentionally captured, the images will be de-identified. The Sponsor will upload images to a secure, limited-access repository, and these images may be used to refine the surgical procedures, provide site training, or for other educational purposes related to the clinical development of VC-02.

7.6. Video of Implantation and Explantation Procedures

Video footage involving subjects may be obtained during the study to visually document and evaluate the implantation and explantation procedures. The Sponsor will notify the Investigator when video is requested and provide instructions for capturing the appropriate images. To maintain subject confidentiality, footage will be limited to the implantation and explantation sites during the procedure and will de-identify any images involving the subject's facial features or any other uniquely identifiable physical features. The Sponsor will upload images to a secure, limited-access repository and these images may be used to refine the surgical procedures, provide site training, or for other educational purposes related to the clinical development of VC-02.

7.7. Ultrasound Monitoring

Ultrasound monitoring will be performed by trained personnel at the clinical site. The central imaging vendor will perform validation of the machine utilized to capture images at each site. For consistency of results, it is recommended the same technician at the site perform all ultrasound evaluations on a subject and that the same machine be used on a subject throughout the trial.

Ultrasound monitoring in this study serves two purposes:

1. Safety evaluations to monitor graft performance; and
2. To pre-identify the anatomical location of implanted units prior to an explantation procedure.

These purposes are discussed in more detail below.

- **Safety Ultrasounds:** [redacted]

  The safety ultrasound images will be captured, transmitted, and analyzed by central imaging vendor. Safety ultrasound images are required at Visit 7 (Week 8), Visit 9 (Week 16), Visit 11 (Week 26), Visit 13 (Week 52), Visit 15 (Week 78), and Visit 17 (Week 104). The central imaging vendor's reports should be evaluated by the Investigator for any clinical significance and addressed in accordance with standards of care. The Investigator may order follow-up or repeat tests for additional evaluation of potentially significant results. The Sponsor should be contacted if additional testing is required.

- **Location Ultrasounds**: These ultrasound evaluations will be performed within three (3) days prior to all scheduled sentinel and/or VC-02-300 unit explantation for surgical planning purposes. The technician locates the unit(s) planned for explant and then outlines its location with surgical marker. This allows the Surgeon to minimize tissue trauma and reduces the likelihood of disturbing adjacent implants. [redacted]

If a safety ultrasound procedure and anatomical location ultrasound are required at the same visit, both can be completed within the same imaging session. Conversely, there may be visits where safety ultrasounds are required but do not correspond to a visit requiring an explant procedure, and therefore, location ultrasounds (surgical marking) are not required (and vice versa). Refer to the Schedule of Assessments for the complete listing of when any ultrasound imaging may be required.

Other clinical studies conducted by ViaCyte investigating a similar product 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, sites will be notified. Further information will be available in the central imaging core lab manual.

7.8. Explantation of VC-02™ Combination Product

[redacted]

[redacted] The VC-02 IFU outlines the sentinel explantation procedure, and the Sponsor will also provide training on the proper surgical technique.

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

7.8.1. Explantation of VC-02-20™ Sentinel Units

All sentinel units will be explanted at time-points to be determined by the Sponsor (refer to the Schedule of Assessments). In both Cohort 1, up to ten (10) VC-02-20 sentinels and in Cohort 2, up to twelve (12) VC-02-20 sentinels may be implanted in a subject. The number of sentinels implanted will be determined by the Sponsor in collaboration with the Investigator and Surgeon. The decision will be based on the available data from previous subjects as well as on the availability of anatomical space for surgical implantation.

7.8.2. Explantation of VC-02-300™ Units

As outlined in the Schedule of Assessments, VC-02-300 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, Ethics Committee, DSMB, or Regulatory Authorities stop the study.

At the discretion of the Sponsor and after consultation with the Investigator, or if a unit is suspected to be malfunctioning or damaged, explantation of [redacted] is allowed at any time post-implant for a subject. Explant of [redacted] occur without requiring the subject to officially withdraw from the study (Section 13.6). Although the sentinel units implanted in subjects are expected to behave similarly to the VC-02-300 units, [redacted] will provide additional data on the status of graft function and cell performance.

7.9. Histological Assessment of VC-02 Combination Product

All explanted VC-02-20 sentinels and VC-02-300 units will be placed immediately in a fixative solution and shipped to the Sponsor for histologic assessment. Explant preparation and shipping instructions will be provided to each site. Systematic, histologic evaluation of sentinel explants will help inform the Sponsor as to the expected performance of the larger VC-02-300 units while the study is ongoing. Histological assessment of the units will be performed by the Sponsor or designee and may include but is not limited to:

[redacted]

[redacted]

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 surgical procedures and technique, the anatomical location of implants, or the perioperative care associated with VC-02. Results from these assessments may be compared to the Sponsor's database [redacted]

7.10. Blood Glucose Monitoring

Throughout the trial, the exogenous insulin requirements of enrolled subjects are managed and titrated by the Investigator (or qualified designee) as needed to maintain glycemic control in conjunction with standards of care. For purposes of this study, the diary entries made by the subjects (e.g., insulin doses, SMBG values, and HE occurrences) are the main sources of information available to the Investigator to assist with treatment decisions. CGM data may be utilized for treatment decisions in accordance with local labeling market approvals.

In addition to Investigator review of glucose trends, insulin dosing, and HE occurrences, the Sponsor will conduct routine reviews of blood glucose data. These data are collected as part of the required study procedures. Subjects record insulin dosing and all HE occurrences on a study diary and glucometer data are electronically downloaded. The data are then available in near real-time for review. If potentially concerning trends are evidenced for an individual subject, the Sponsor will notify the Investigator and request for follow-up with the subject to occur if necessary.

Blood glucose monitoring is performed through various methods during the study to ensure proper glucose control:

- Laboratory tests (Sections 7.2, 7.3, and 7.11)
- Continuous Glucose Monitoring (Section 7.10.2)
- Self-Monitoring Blood Glucose (Section 7.10.3)

Data from these methods will be available to the Investigator via reports from laboratories, study diaries, and downloads or entries from CGM and SMBG meters to facilitate treatment decisions. The glucose monitoring data collected between Visit 2 (Week -4) and Visit 3 (Day 1) establishes the baseline profile of each subject's glycemic control (e.g., the percent time spent at various blood glucose cutpoints per CGM data, SMBG blood glucose levels, exogenous insulin doses, and frequency of HEs).

During the study, decreasing requirements for exogenous insulin may be achieved gradually as cells differentiate into mature, insulin-secreting cells. This reduction in exogenous insulin dose typically is expected to occur over a period of three (3) to six (6) months post-implantation, but may occur later in some patients. In addition to the requirement for frequent review of the available sources of subject-reported data, Investigators are encouraged to engage in routine contact with subjects (e.g., phone calls, texts, and emails) and/or schedule Unplanned Visits between the

protocol-required visits to facilitate insulin adjustments and to address any potential safety issues as needed.

A study reference manual may further outline the various logs and data collection portals available to the Investigator.

7.10.1. Study Diary

Starting at Visit 2 (Week -4) and throughout the duration of participation in the trial, subjects are required to enter or download all SMBG values, HE occurrences and associated symptoms, and insulin doses into the study diary on a daily basis. Because treatment decisions are based, in part, on the availability of this information, the Investigator must make all reasonable efforts to ensure subjects comply with the requirement for daily entry of this important information. After implantation, if a subject demonstrates repeated non-compliance with this requirement, the Investigator must document efforts to correct and prevent future non-compliance in the subject source records.

At a minimum, diary data must be reviewed by the Investigator at each study visit to determine if insulin dosing should be modified. Review of available study diary data at each visit must be documented in the subject source records. Subject diary entries may also be available for review in near real-time by the Investigator using secure cloud technology, and automated e-mail alerts may be configured for alert to the Investigator for occurrences of potential safety-related issues (e.g., if a SHE is reported or if the frequency of HEs reported within a certain period requires further evaluation).

7.10.2. Continuous Glucose Monitoring (CGM)

All subjects will be provided with a CGM system. Previous experience with CGM is not a requirement of study entry, but all subjects are required to use the Sponsor-provided CGM during study participation. Based on the labeled indication of the CGM in use, diabetes treatment decisions may be based on CGM data collected. Subjects relying on CGM data for treatment decisions will be required to be compliant with CGM usage and wear the CGM for the entire two-year study and also periodically sync the data, so that near-real time access may be available to the Investigator and Sponsor. A study reference manual will further outline the logistics with respect to CGM use and data collection.

All CGM supplies and instruction manuals will be provided by the Sponsor. Site personnel will instruct the subject on proper use and care at Visit 2 (Week -4) and as needed throughout the study. This training includes assisting the subject with the insertion of the first sensor needle prior to leaving the clinic at Visit 2. The CGM system is configured to alert the subject in the event blood glucose values approach hypoglycemic levels.

The CGM data collected for this trial will be used to evaluate secondary and exploratory endpoints. 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 <54 mg/dL, ≥54 to <70 mg/dL, ≥70 mg/dL to ≤180 mg/dL, and >180 mg/dL). Other endpoints using CGM data may be evaluated and, if so, will be described in the Statistical Analysis Plan (SAP).

7.10.3. Self-monitoring Blood Glucose (SMBG)

SMBG supplies including a Sponsor-provided portable meter, test strips, lancets, control solution, and sharps containers will be provided and required for use by each subject starting at Visit 2 (Week -4). Instructions for routine SMBG monitoring via fingerstick and calibration of the meter will be provided to each subject. The recommended frequency of SMBG monitoring will be determined for each subject by the Investigator. All SMBG values, whether conducted for routine blood glucose monitoring, confirmation of hyperglycemia or hypoglycemia, or due to the calibration requirements of the CGM equipment, will be logged on a study diary.

7.10.4. Definition, Classification, and Management of Hypoglycemic Events (HEs)

All SMBG or CGM values of <54 mg/dL must be captured by the subject in the diary as a HE. Additionally, if a subject does not have a blood glucose value available, but has symptoms of a HE, the HE must still be captured in the diary as an HE. ***For any 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.***

At Visit 3 (Day 1) and each clinic visit thereafter, the Investigator will review the subject's HE entries on the study diary, CGM and SMBG values, and any other supportive information. Each HE occurring beyond Visit 2 (Week -4) must be captured on a CRF and will be classified based on the definitions below. Per standards of care, the Investigator should also evaluate any HEs occurring between Visit 1 and Visit 2 reported by the subject, 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 <54 mg/dL (3.0 mmol/L) in the absence of symptoms.
- Probable symptomatic hypoglycemia: subject reports typical hypoglycemia symptoms but does not provide a temporally-associated SMBG or CGM value.
- Pseudo-hypoglycemia or relative hypoglycemia: an event is reported by subject, but the associated SMBG or CGM value is ≥70 mg/dL (3.9 mmol/L).

The frequency of HEs will be captured and counted over the course of the study. In addition, the Sponsor will consider defining additional HEs using the CGM data on an exploratory basis. The Investigator may request an Unplanned Visit to review study diary entries and determine if modifications in insulin dosing are necessary to reduce the occurrence of HEs. Based on available information, the Investigator should make appropriate decisions regarding the insulin therapy to mitigate HE occurrences.

7.11. Laboratory Evaluations

Central laboratories identified by the Sponsor will test the majority of protocol-required, biological samples collected from subjects in the study. Details regarding the laboratory specimen preparation, handling, storage, shipping and reporting procedures will be outlined in a separate laboratory reference manual. All protocol-required samples will be collected at the time-points indicated on the Schedule of Assessments.

As needed (e.g., immunosuppression drug levels, absolute lymphocyte counts [to confirm adequate pre-implant immunosuppression has been achieved], or urgent medical events), local laboratories available to a site may be utilized.

All laboratory test results outside of normal range should be evaluated by the Investigator for any clinical significance and addressed in accordance with standards of care. The Investigator may order repeat tests once for additional evaluation of potentially significant results. The Sponsor should be contacted if additional testing is required after repeat tests have been conducted.

7.11.1. Routine Clinical Laboratory Evaluations

Subjects will have routine laboratory assessments performed throughout the study, including:

- Hematology: hemoglobin, hematocrit, RBC count, platelet count, WBC count, total neutrophils, eosinophils, monocytes, basophils, and lymphocytes.
- Chemistry: 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.

  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.
- Fasting serum lipid panel: 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.
- Urinalysis (central lab dipstick): pH, protein, blood, ketones, leukocyte esterase, and nitrites. Microscopy is done if the 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.
- Serology: screening for HB core and sAg/Ab, HCV, HIV (1&2), CMV IgG, and EBV IgG. Subjects are also tested post-implant via CMV PCR at Weeks 12 and 26. Additional CMV

IgG and IgM testing is completed at Week 52 and Week 104 *only if previous CMV testing was negative*.

- Other: HbA1C, ultrasensitive C-peptide (collected in conjunction with MMTTs pre-stimulation (time = 0) and post-stimulation at a 90 minute [+/- 10 minutes] timepoint), urine pregnancy tests, Quantiferon, renal function evaluation via MDRD eGFR calculation, and TSH (screening).

7.11.2. Pregnancy Tests

A urine pregnancy test is administered to all women at Visit 1 (Week -5), at Visit 3 (pre-implant), and post-implant at Visit 13 (Week 52) and Visit 17 (Week 104) or early termination. However, additional pregnancy tests may be completed if the Investigator suspects a possible pregnancy, as per request of the Ethics Committee, or if required by local regulations.

7.11.3. Immunosuppression Drug Levels and Safety Labs

Certain drugs prescribed as part of each subject's immunosuppressive regimen may require additional blood testing to ensure appropriate concentrations are achieved to facilitate the engraftment and long-term function of implanted VC-02 units. Routine testing of concentration levels is required to avoid drug toxicity and any associated adverse events. Refer to Section 5.2 for details on the planned immunosuppression regimen.

Based on the immunosuppression regimen prescribed for the patient, and after discussions between the Sponsor and Investigator, the target concentration of each applicable drug, as well as the frequency of any additional blood testing required to obtain concentration results and assess safety (e.g., additional hematology and chemistry testing), will be included as part of the implantation strategy plan for the subject. Blood collections required to measure immunosuppression drug levels may be collected at regularly scheduled protocol visits or at an Unplanned Visit as needed, depending on the frequency of the required drug concentration monitoring.

7.11.4. Immune Panel

Blood samples for humoral and cellular immunity testing will be obtained at specific time-points throughout the trial as listed in the Schedule of Assessments. The panel of immune function tests includes those 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 may 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 specific hours to maintain stability of the sample. If needed, these samples can be collected on a day prior to the remainder of the visit in order to meet the stability requirements, but within the protocol-allowed visit windows. The baseline sample may be collected at any time between Visit 2 and Visit 3 once determined the subject qualifies for the study. Additional details are provided in a separate laboratory manual.

7.11.5. Reserve Blood Samples

Additional blood samples from subjects may be collected starting at Visit 2 and at up to four (4) additional study visits for investigational assessment of biomarkers that could be associated with the cellular viability and durability of the implanted VC-02 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 5 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 may be provided in a separate laboratory manual.

7.11.6. Blood Volumes

Total blood collection volumes from scheduled visits requiring lab assessments are not planned to be greater than 700 mL over the course of the trial. Of the 18 clinic visits, there are five (5) visits where blood volumes are estimated to be up to approximately 80 mL: Visit 2 (Week -4), Visit 11 (Week 26), and Visit 13 (Week 52), and Visit 17 (Week 104). At other visits, the blood volume required ranges from 0 mL to 60 mL.

If all allowed reserve blood samples (Section 7.11.5) are collected, this would result in up to an additional 25 mL of blood collected during the trial.

Additionally, it is expected that up to approximately 15 mL of blood may be collected each time the site tests the immunosuppression drug concentrations and the associated safety tests.

For all subjects, blood collections are not planned to occur more frequently than once per week unless there is a need for an Unplanned Visit.

7.12. Clarke Survey

The Clarke Hypoglycemia Unawareness Survey (Appendix 1) is a validated scoring system used to measure the degree of awareness a subject with T1DM has to symptoms associated with hypoglycemia (Gold, Macleod, & Frier, 1994). It will be administered at Screening Visit 1 to determine if the inclusion criterion (score ≥ 4) is met. Subjects will then complete the Clarke Survey at the following additional time points: Visit 9 (Week 16), Visit 11 (Week 26), Visit 12 (Week 39), Visit 13 (Week 52), Visit 15 (Week 78), and Visit 17 (Week 104).

8. SAFETY REPORTING

The Investigator is required to report all directly-observed AEs, all spontaneously reported AEs, and any pregnancies experienced by study subjects. 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;
- Sensitization to the [redacted];
- Progression/worsening of underlying disease (includes worsening diabetes, as assessed by the Investigator)

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 the Sponsor and the Ethics Committee. 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 the Sponsor 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 a 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 Common Terminology Criteria for Adverse Event (NCI-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.

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). In relation to implantation with VC-02, there are three (3) main components to assessing causality. The Investigator's causality assessment must include a determination of whether there exists a reasonable possibility that:

- The investigational product (VC-02) itself caused or contributed to the AE.
- The surgical procedure (implantation or explanation) caused or contributed to the AE.
- The immunosuppression drug regimen caused or contributed to the AE.

In evaluating the causal relationship of an AE to VC-02, the surgical procedures, and the immunosuppression regimen, it is possible for the Investigator to determine causality as being associated to one or more of these factors. Conversely, the Investigator can determine that none of these relate to the AE.

If the Investigator's final determination of causality is unknown, and the Investigator does not know if the investigational product, surgical procedure, or immunosuppression drugs caused the event, then the event will be classified 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 VC-02, the surgical procedures, and the immunosuppression drugs 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, the surgical

procedures, or the immunosuppression drugs, 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, the surgical procedures, or the immunosuppression drugs, but which could also be explained by concurrent disease or other drugs or chemicals.

Definitely Related: A clinical event, including laboratory test, occurring in a plausible time relationship to the investigational product exposure, surgical procedures, or the immunosuppression drugs, and which cannot be explained by concurrent disease or other drugs or chemicals.

8.1.2. Expected Adverse Events

Refer to Section 1.4.1.

8.1.3. Determination of Abnormal Laboratory Test Values or Abnormal Clinical Findings as Adverse Event

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 is not associated with a known, pre-existing condition or part of the subject's medical history, 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. An abnormal test result determined to be an error does not require reporting as an AE.

Evidence of product sensitization (the presence of donor anti-HLA antibodies absent prior to implant) is not in itself considered an AE. The above criteria should also be utilized to determine if the sensitization qualifies as an AE.

8.1.4. Adverse Events of Special Interest (AESI)

Certain AEs may require additional investigation to ensure appropriate information and data are captured to appropriately evaluate the clinical development of VC-02. These are considered adverse events of special interest (AESI) and may include but are not limited to:

- AEs leading to the unexpected or premature explantation of VC-02-300 or sentinel units are considered AESI.
- AEs that result in early withdrawal from the study.

- Severe hypoglycemic events occurring after VC-02 implantation possibly or definitely related to VC-02.

If an AESI occurs, the Sponsor may request that additional data be collected for these events.

8.1.5. Period of Observation and Reporting

All AEs with a start date occurring between Visit 2 (Week -4) and through the last subject visit must be recorded on the CRF. During the study, sites should query subjects on the status of any ongoing AEs at subsequent clinic visits. Depending on the reported event, the Investigator may need to follow-up on the status of AEs with the study subject between visits (e.g., phone, text, or email). At the conclusion of the trial, any ongoing AEs will be followed until at least 28 days after the final explantation procedure to determine the final reported outcome of the event.

For SAEs, including pregnancy reports, the active reporting period to the Sponsor begins from the time the subject provides informed consent through and including 28 days after the final explantation of all of the investigational product units.

SAEs occurring after the period of observation has ended should be reported to the Sponsor if the Investigator becomes aware of an event. At a minimum, all SAEs the Investigator assesses as possibly related to the investigational product are to be reported to the Sponsor.

The reporting period for AEs and SAEs may overlap with the timing of the subject's participation in the mandatory, long-term follow-up study. Further details on how to report ongoing AEs spanning the period between the VC02-101 protocol and follow-up study will be outlined in the separate follow-up protocol.

All AE reporting, including SAEs and SUSARs, will be carried out in accordance with applicable regulations.

8.2. Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence meeting at least one of the following criteria:

- 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 in the opinion of the Investigator and/or Sponsor.

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 the event may jeopardize the subject or may require intervention to prevent one of the other SAE criteria, 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 classified at the Investigator's discretion. In all instances, SHEs are to be recorded on the hypoglycemic event (HE) CRF.

AEs resulting in hospitalization or prolongation of a hospitalization are considered serious. Any formal admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute or 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;
- Emergency room visits;
- Outpatient surgical 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 pre-existing 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 medical history assessment and documentation for an 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. Suspected, Unexpected Serious Adverse Reactions (SUSAR)

A SUSAR is a serious adverse reaction which is thought to be causally related to the investigational product, surgical procedure, and/or immunosuppression regimen and which is unexpected to occur. Reporting of SUSARs to the Sponsor, all participating Investigators, the Ethics Committee, and to the Regulatory Authorities is mandatory in accordance with applicable regulations.

Because of the limited shelf-life of the investigational product, the results of the 14-day sterility testing of VC-02 are not available until after implantation occurs. In the unexpected event of positive culture results from this test, the Sponsor will notify the Investigator, who will then notify the subject. The Sponsor will initiate further testing of the positive sample to identify the microorganism and conduct a root-cause analysis. The Investigator 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.

8.2.2. SAE Reporting Procedures

If an SAE occurs, the Sponsor must be notified within 24 hours of the Investigator becoming aware of the occurrence of the event. In particular, if the SAE is fatal or life-threatening, notification to the Sponsor must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional, new information (follow-up) on previously reported SAE reports as well as to the initial and follow-up reporting on cases of exposure during pregnancy and exposure via breastfeeding.

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

For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific, additional, follow-up information in an expedited fashion. The information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the SAE 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 event of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor.

8.3. Reporting of Pregnancy

For investigational products, an exposure during pregnancy (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 VC-02 units implanted, this will also be captured as an EIU. Pregnancy itself is not an AE. However, adverse consequences of pregnancy should be reported as an AE or SAE as applicable.

If the subject or the subject's partner becomes or is found to be pregnant during the study, the Investigator must submit this information to the Sponsor 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 recorded in a Pregnancy Registry.

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the Sponsor 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 include:

- 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.
- Death of an infant older than one month should be reported as an SAE if the Investigator assesses the infant death as related or possibly 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. 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 study 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 minutes and provided to the Sponsor. When necessary, summary DSMB minutes may be distributed to participating sites for submission to Ethics Committees. A separate DSMB Charter will direct the activities of the Board.

The approximate timing of DSMB meetings are noted below:

- After a minimum of three (3) subjects from Cohort 1 have reached the Week 4 clinic visit and the results are available, the Sponsor then has the ability to request the DSMB to meet. The available cumulative data collected in all subjects from Cohort 1 up until that time will be evaluated by the DSMB. Based on review of the available data, the DSMB will make a recommendation on the enrollment of Cohort 2. The DSMB will not meet regularly during Cohort 1 unless there is a related AE that requires an independent DSMB review.
- Quarterly during the first year of Cohort 2, and thereafter every three (3) to six (6) months until the last visit of the last Cohort 2 subject has occurred.

Additional meetings of the DSMB may be scheduled based on data review needs or by request.

8.5. 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 will recommend stopping the study for any of the following:

1. Two or more subjects have pronounced immune responses to VC-02.
2. Two or more subjects experiencing a NCI-CTCAE Grade 3 (severe) 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 VC-02. This assumes the SHE occurred despite reasonable adjustments in the exogenous insulin requirements and appropriate dietary adjustments.
4. Two or more subjects develop SAEs deemed related to the implantation of VC-02 itself; 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 these events, the DSMB can consider recommending a temporary delay or hold on enrollment in the trial for events considered by the Investigator to be related to VC-02. The DSMB can also recommend treatment continue for a shorter duration (i.e., less than the planned two years) or with a fewer number of implanted units. The DSMB can also recommend 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 Ethics Committee will make the ultimate decision to delay enrollment, modify treatment duration, or stop the study based on DSMB recommendations.

The Sponsor may also decide to terminate the study for other safety or lack of efficacy reasons. In the event the study is terminated, all subjects will have their VC-02 units explanted, and all subjects will be followed post-explant in a long-term follow-up study (VC02-201).

9. CLINICAL MONITORING

Routine monitoring of investigative sites by the Sponsor 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 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 issues detected are appropriately addressed and resolved. It is important that the Investigator 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. An associated monitoring plan will outline items to be monitored and the frequency of monitoring.

10. STATISTICAL CONSIDERATIONS

Methodology for the summarization and analysis of the data collected in this trial are given here and further detailed in a SAP, which will be maintained by the Sponsor. The SAP may be written and approved prior to the Cohort 1 data cut-off (e.g., the last subject in Cohort 1 completing the Week 4 visit whose data is part of the DSMB data review), since this time-point will trigger a DSMB review of the accumulated data and result in a recommendation for enrollment of Cohort 2.

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-02-300 units. If a subject has a VC-02-300 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-02-300 units originally implanted. If no VC-02-300 units are implanted, but sentinel units are implanted, then the subject will be included in the “0 implanted VC-02-300 units” treatment group.

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 fifteen (15) subjects will be enrolled in Cohort 1. Approximately 60 subjects will be enrolled in Cohort 2, for a total enrollment of up to 75 subjects in both cohorts.

Sample size in Cohort 1 was empirically derived, based upon safety considerations and data accumulated from previously performed ViaCyte clinical trials. A sample size of up to 15 subjects should allow for adequate assessment of Cohort 1 study objectives.

A sample size of 60 subjects in Cohort 2 will enable staggered enrollment of cadres of subjects allowing for testing of alternate device configuration and/or surgical implant technique (e.g., pharmacological intervention, implant site, etc.) in order to improve engraftment and cell survival outcomes. This approach will drive VC-02 engraftment optimization.

Once the optimized device configuration and surgical implant technique is determined, a sample size of 40 subjects implanted [redacted] Since Cohort 1 has the primary objective of evaluating initial safety and tolerability, these subjects will not contribute MMTT data for the Week 26 analysis.

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. A sample size of 40 subjects [redacted]

For the 2-hour MMTT, a sample size of 40 subjects will provide [redacted]

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. The DSMB will review all accumulated data when at least a minimum of three (3) Cohort 1 subjects complete the Week 4 visit, in order to make a recommendation on enrollment of Cohort 2. In addition, 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 8.4 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 11 (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.

The Sponsor will perform a risk/benefit assessment at 9-12 months post-implant for each Cohort 2 subject and at other time points, as warranted. This assessment evaluates each individual subject's data in order to determine whether that subject should continue taking chronic immunosuppression and remain in the study or whether all units will be explanted. Factors evaluated include C-peptide concentration, histology from a sentinel device explanted at approximately nine (9) months, change from baseline in average weekly insulin administration, change from baseline in HbA1c, change from baseline in frequency of hypoglycemic events, change from baseline in Clarke Score, change from baseline in time-in--range, compliance with immunosuppression, as well as adverse events and other safety findings. In cases where a subject is early terminated from the study as a result of the risk/benefit assessment, specific early termination visit procedures (i.e., the 4-hour MMTT and safety ultrasound) will not need to be repeated if they were recently performed (within the last 8 weeks).

10.4. Analysis Details

10.4.1. Analysis Populations

The Full Analysis Set (FAS) is defined as all subjects from Cohort 2 who were enrolled into the study and received implantation of at least one VC-02-300 or sentinel unit on Study Day 1. All efficacy summaries/analyses will be performed on the FAS. Subjects will be summarized by Cohort and treatment group.

The Safety Analysis Set (SAS) will include all subjects from Cohort 1 and Cohort 2 who were enrolled into the study and in whom an implant surgery was attempted, regardless of whether any VC-02-300 units or sentinel-sized units were actually implanted. This includes all subjects in both Cohorts. 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 (for both Cohort 1 and Cohort 2 subjects who meet the SAS criteria) will be used for the primary safety summarizations. Adverse events and SAEs will be summarized by 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-02-300 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 to Week 26 in C-peptide $AUC_{0\text{-}4h}$ following an MMTT 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 will be used to analyze the primary efficacy endpoint, with the ANCOVA performed within each Cohort. 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.

10.4.5.1. Secondary Efficacy Analyses

The FAS will be used to analyze the secondary efficacy endpoints, with the analysis for each endpoint performed within each Cohort. 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 16, 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.

Change from baseline in frequency of hypoglycemic events (24-hour; daytime [start between 6 a.m. – 12 a.m.]; nocturnal [start between 12 a.m. – 6 a.m.]) at Weeks 16, 26, 52, 78; change from baseline to Weeks 16, 26, 52, 78 and 104 in Clarke score; and change from baseline to Weeks 16, 26, 52, 78 and 104 in average daily insulin dose in the seven days preceding the clinic visit 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 achieving a positive stimulated C-peptide (defined as > 0.2 ng/mL) after implant; the percent of subjects free of severe hypoglycemic events from Week 16 to Weeks 20, 26, 39, 52, 78 and 104; the percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose from baseline to Weeks 16, 20, 26, 39, 52, 78, and 104; the percent of subjects who achieve exogenous insulin independence; the percent of subjects who achieve exogenous insulin independence and an HbA1c < 7.0% 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 will be provided (at each timepoint, where appropriate).

Percent of time spent with blood glucose values at various cut points at each scheduled visit will be summarized descriptively. The percentages and change from baseline percentages will be

summarized for each cut point (<54 mg/dL, ≥54 to <70 mg/dL, ≥70 mg/dL to ≤180 mg/dL, and >180 mg/dL) and for each treatment group.

10.4.5.2. Secondary Safety Analyses

Unless otherwise specified, the SAS (both Cohort 1 and Cohort 2 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 Ethics Committee 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 Ethics Committee. 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. Ethics Committees

An Ethics Committee 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 Ethics Committee. All correspondence with the Ethics Committee should be retained in the Investigator File. Copies of Ethics Committee approvals should be forwarded to the Sponsor.

The Institution shall have no ability to alter, amend or modify the protocol. The only circumstance in which an amendment may be initiated without Ethics Committee 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 Ethics Committee 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 Ethics Committee, 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.

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 17 (Week 104) as well as the procedures outlined in follow-up Visit 18 (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 Investigator 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-02. This assumes the SHE occurred despite reasonable adjustments 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-02.
- Subject appears to mount an immune or inflammatory response that puts the subject at risk for severe or serious 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 to facilitate continued participation.
- Subject becomes pregnant or in the Investigator's opinion is non-compliant with contraception requirements (see Section 5.4.5).
- Due to the recommendation based upon the outcome of a risk/benefit assessment (see Section 10.3.2).
- Implanted units appear to be damaged or malfunctioning (e.g., localized infections, damaged unit) resulting in severe or serious AEs. 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-02-300 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-02-300 units and any remaining sentinel units will be explanted. The subject will be asked to follow-up with the study site post-explant in the long-term follow-up study.

13.6.1. Handling of Withdrawals

Subjects who are withdrawn prematurely from the study will have the VC-02-300 units and sentinels 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 three (3) attempts by telephone and at least three (3) attempts by certified letter should be made to contact the subject. 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 all circumstances, 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 the VC-02-300 units and sentinels.

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 long-term, follow-up trial. Those subjects may initiate any other therapy as needed to treat diabetes and any other concurrent medical conditions.

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response and recorded on the appropriate AE CRF page. When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined in Section 8. The reason for discontinuation will be documented in the subject's source records.

For safety reasons, all early termination procedures (including explantation procedure) as described in Visit 17/ET and Visit 18 should be performed if a subject discontinues the trial.

13.7. Study Discontinuation

In the event the entire study is stopped prematurely, the Sponsor will notify all Investigators, the Ethics Committees, and applicable Regulatory Authorities of the decision to discontinue the study. The reasons for discontinuing the trial will be communicated to the Investigators in a written document, and the Investigators will then provide this information to all active subjects, and as required, submit the information to the Ethics Committee. If the reasons for discontinuing the trial potentially affect subjects who have already completed participation in the trial, the Investigator may be required to contact those subjects to provide information as per local requirements.

The Investigator will schedule all remaining, active subjects as soon as reasonably possible for completion of the Visit 17 (ET) and Visit 18 procedures. These procedures should be completed as described for early withdrawal subjects in Section 13.6.1.

13.8. Future Evaluation of Explanted Units

Evaluation of the explanted units is previously described. However, evaluated units may 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, 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), 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 there may be deviations resulting from circumstances beyond control or unintentional oversights or mistakes. 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 documented by the Investigator and reviewed by the Sponsor. Corrective actions will be put into place to prevent future occurrences of deviations, if possible. These deviations from the protocol must be documented at the site, and the Sponsor must be notified. Depending on the particular EC used at each site, notification of the EC 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

Appendix 1: Clarke Hypoglycemia Unawareness Survey

1. Check the category that best describes you: (check one only)

	I always have symptoms when my blood sugar is low	A
	I sometimes have symptoms when my blood sugar is low	R
	I no longer have symptoms when my blood sugar is low	R

2. Have you lost some of the symptoms that used to occur when your blood sugar was low?

	Yes	R
	No	A

3. In the past six months how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself)

	Never	A
	Once or twice	R
	Every other month	R
	Every month	R
	More than once a month	R

4. In the past year how often have you had severe hypoglycemic episodes? (Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose)

	Never	A		5 times	R		11 times	R
	1 time	R		6 times	R		12 times or more	R
	2 times	R		7 times	R			
	3 times	R		8 times	R			
	4 times	R		9 times	R			

5. How often in the last month have you had readings < 70 mg/dL (3.8 mmol/L) with symptoms?

	Never		1 time/week		4 to 5 times/week
	1 to 3 times		2 to 3 times/week		Almost daily

6. How often in the last month have you had readings < 70 mg/dL (3.8 mmol/L) without symptoms?

	Never		1 time/week		4 to 5 times/week
	1 to 3 times		2 to 3 times/week		Almost daily

If answer to question 5 < answer to question 6	R
If answer to question 6 ≤ answer to question 5	A

7. How low does your blood sugar need to go before you feel symptoms?

	60-69 mg/dL,	3.3 - 3.8 mmol/L	A
	50-59 mg/dL;	2.8 – 3.3 mmol/L	A
	40-49 mg/dL;	2.2 – 2.7 mmol/L	R
	less than 40 mg/dL	less than 2.2 mmol/L	R

8. To what extent can you tell by your symptoms that your blood sugar is low?

	Never	R
	Rarely	R
	Sometimes	R
	Often	A
	Always	A

Final score: Total Number of "R" responses: _____

Interpretation: Four or more "R" responses = reduced awareness; 2 or fewer "R" responses= aware