# VC01-103

# An Open-Label, Phase 1 / 2 Study to Evaluate the Safety, Engraftment and Efficacy of VC-01™ Combination Product in Subjects with Type 1 Diabetes Mellitus

## Study Protocol

## Final Version 4.0

## 29 Sep 2020

## ViaCyte Inc.

## NCT04678557

# AN OPEN-LABEL, PHASE 1/2 STUDY TO EVALUATE THE SAFETY, ENGRAFTMENT AND EFFICACY OF VC-01™ COMBINATION PRODUCT IN SUBJECTS WITH TYPE 1 DIABETES MELLITUS

| | |
|---|---|
| **Protocol Number** | VC01-103 |
| **Compound** | PEC-01™ cells with Encaptra® Drug Delivery System [together known as VC-01™ Combination Product] |
| **Study Phase** | 1/2 |
| **Sponsor Name and Address** | ViaCyte Inc., 3550 General Atomics Ct., San Diego, CA 92121 |
| **Version Number** | 4.0 |
| **Version Date** | September 29, 2020 |
| **Amendment Number** | 03 |

# TABLE OF CONTENTS

# PROTOCOL SUMMARY

| | |
|---|---|
| **Title:** | An Open-Label, Phase 1/2 Study to Evaluate the Safety, Engraftment and Efficacy of VC-01™ Combination Product in Subjects with Type 1 Diabetes Mellitus (T1DM) |
| **Phase:** | 1/2 |
| **Population:** | Subjects with T1DM will be enrolled into this clinical trial.<br>Total enrollment will be up to 70 subjects.<br>Cohort 1: Up to 30 subjects<br>Cohort 2: Up to 40 subjects |
| **Number of Sites:** | Up to approximately ten (10) |
| **Study Duration:** | The total duration of the trial is estimated to be up to approximately 48 months or four (4) years:<br>**Cohort 1**<br>• Approximately 18 months to complete enrollment of all subjects.<br>• An additional six (6) months from the time the last subject is enrolled until the last subject last visit.<br>**Cohort 2**<br>• Approximately 12 months to complete enrollment of all subjects.<br>• An additional 12 months from the time the last subject is enrolled 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 follows:<br>**Cohort 1**<br>• Approximately seven (7) months per subject, inclusive of:<br>o Approximately (2) week screening period<br>o Up to six (6) months duration of treatment<br>o One (1) week follow-up post final explant<br>**Cohort 2**<br>• Approximately 13 ½ months per subject inclusive of:<br>o Up to five (5) weeks screening period<br>o Up to 12 months duration of treatment<br>o One (1) week follow-up post final explant |

For both Cohort 1 and Cohort 2, after all VC-01 units have been explanted, each subject will be requested to participate in a separate, long-term, follow-up study protocol.

**Description of Agent or Intervention:**

ViaCyte is developing VC-01 combination product (VC-01™) which is intended to control blood glucose in a more physiologic, sensitive, and homeostatic manner than the various forms of injectable insulin and pump therapies currently available. VC-01 combination product is comprised of two components: (1) PEC-01 pancreatic endoderm cells derived from human embryonic stem cells (hESC) and (2) a durable, cell-impermeable, removable, macroencapsulation device known as the Encaptra drug delivery system (EDDS). Throughout this study, a series of EDDS configurations may be assessed to improve engraftment and cell survival outcomes. It is anticipated that more than one version of the EDDS may be used in this study; hence the term "EDDS configuration" represents a unique version of the EDDS.

Following [redacted] implantation [redacted], the VC-01 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-01-DF combination product ("DF" refers to dose-finding) and smaller sentinel combination product; these are smaller units that will be explanted at various time points and examined histologically *ex vivo*.

**Study Design:**

This will be an open-label clinical trial in subjects with T1DM. Two cohorts are planned for enrollment in this trial:

**Cohort 1– Safety and Engraftment**

Up to 30 subjects may be enrolled and receive subcutaneous implantation of up to ten (10) sentinel units. The sentinel units may be explanted at varying time points post-implant to assess graft cell viability, differentiation, vascularization, and host response.

Total duration of treatment may be up to six (6) months for each Cohort 1 subject, with the last unit explanted at Month 6 /Week 26 or earlier if requested by the Sponsor. Cohort 1 subjects will complete a total of up to 12 study visits.

After a minimum of three (3) subjects have been enrolled in Cohort 1 and have completed through Week 4, the Sponsor then has the ability to initiate enrollment of Cohort 2 and request the DSMB to review the completed Cohort 1 data for safety, tolerability, and proof of mechanism.

**Cohort 2 – Safety and Efficacy**

Upon confirmation of histological response in Cohort 1 subjects, demonstrating engraftment and the potential for clinical efficacy at a higher (therapeutic) dose, enrollment in the Efficacy Cohort 2 will be initiated.

Up to 40 subjects may be enrolled and receive subcutaneous implantation of:

- Up to nine (9) VC-01-DF units, or;
- Up to 12 units total. Of the 12 units, no more than nine (9) will be VC-01-DF and the remainder will be sentinel units. For example, if seven (7) VC-01-DF units are implanted in a subject, up to five (5) sentinels may be implanted.

The sentinel units may be explanted at varying time points post-implant to assess graft cell viability, differentiation, vascularization, and host response. At the discretion of the Sponsor and after consultation with the Investigator, explantation of up to two (2) VC-01-DF units is allowed at any time post-implant without needing to withdraw the subject from the study.

Total duration of treatment may be up to one (1) year for each Cohort 2 subject, with the last unit explanted at Month 12/Week 52 or earlier if requested by the Sponsor. Cohort 2 subjects will complete a total of up to 14 study visits.

**Study Objectives:**

This trial will test if VC-01 combination product can be implanted and maintained with safety, tolerability, and efficacy for up to Month 12/Week 52. There are two Cohorts in this trial with the following study objectives:

**Cohort 1**

Primary Objective:

- Assess via histology the potential for functional engraftment of VC-01 combination product when implanted into subjects with T1DM.

Secondary Objectives:

- Assess via histology the host immune response to VC-01 combination product when implanted into subjects with T1DM.
- Evaluate the safety and tolerability of VC-01 combination product from implantation to Month 6/Week 26 or earlier if requested by the Sponsor.

**Cohort 2**

Primary Objective:

- Evaluate the clinical efficacy of VC-01 combination product from implantation to Month 12/Week 52 or earlier if requested by the Sponsor.

Secondary Objectives:

- Further assess safety and tolerability of VC-01 combination product from implantation to Month 12/Week 52 or earlier if requested by the Sponsor.

Exploratory Objectives:

- Further assess via histology the potential for functional engraftment of VC-01 combination product when implanted into subjects with T1DM.
- Explore effects of weight, gender, BMI, or other potentially interacting factors on the responsiveness of the subjects to the experimental intervention.
- Optimize the recommended surgical implantation procedure, anatomical location, and peri- and post-operative care for VC-01.
- Further assess the effects of the host immune response to implanted VC-01 units.

**Study Endpoints:**

The study endpoints for each cohort are as follows:

**Cohort 1**

Primary Endpoint Measures:

- The percentage of viable graft cells at post-implant time points relative to pre-clinical models.
- The percentage of graft cells staining positive for markers of beta cells at post-implant time points relative to pre-clinical models.

Secondary Endpoint Measures:

- The qualitative assessment of the severity of the host immune response as rated at post-implant time points.
- The comprehensive safety profile of VC-01 implanted for up to six (6) months as measured by:
    - All reported adverse events (AEs).
    - The incidence of subjects requiring a premature explant due to safety issues.
    - The incidence of off-target growth as evidenced by implanted VC-01 units via lumen ultrasound measurements, or by histological examination of explants.
    - The incidence of immune sensitization defined by presence of donor anti-HLA (human leukocyte antigen) antibodies absent prior to implant.

**Cohort 2**

Primary Endpoint Measure:

- Change from baseline to Week 26 in C-peptide area under the curve from 0 to 4 hours ($AUC_{0\text{-}4h}$) following a Mixed Meal Tolerance Test (MMTT).

Secondary Endpoint Measures:

*Safety and Tolerability*

- Comprehensive profile of VC-01 combination product implanted for up to Month 12/Week 52 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) 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 8, 12, 16, 20, 26, 39, and 52 in C-peptide $AUC_{0\text{-}2h}$ and change from baseline to Week 52 in C-peptide $AUC_{0\text{-}4h}$ following an MMTT.
- Change from baseline to Weeks 16, 20, 26, 39 and 52 in average daily insulin dose in the 7 days preceding the clinic visit.
- 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.
- Percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose from baseline to Weeks 16, 20, 26, 39, and 52.
- 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, >180 mg/dL and >250 mg/dL) as measured by each subject's continuous glucose monitor (CGM)
- Change from baseline to Weeks 16, 20, 26, 39 and 52 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 and >250 mg/dL) as measured by each subject's CGM

*Exploratory*

- 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:**

**Cohort 1 and Cohort 2**

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject has been informed of all aspects of the trial and agrees to participate in the trial
2. Men and non-pregnant women 18-65 years of age.
3. Diagnosis of T1DM for a minimum of three (3) years.
4. Stable, optimized diabetic regimen for at least 3 months.
5. Acceptable candidate for implantation and explantation procedures as assessed by Investigator
6. Willing and able to comply with scheduled visits, treatment plans, post-surgical care and restrictions, laboratory tests, and other study procedures.
7. All male subjects and female subjects of childbearing potential must practice highly-effective contraception, as described in **Section 5.4.4** during the study and be willing and able to continue contraception until final explant.

**Cohort 2 Only**

8. Insulin dosage at screening <1 unit/kg/day (using previous seven days as average).
9. Willing to use a provided CGM System.
10. Willing and able to comply with daily entries on a study diary.

**Exclusion Criteria**

**Cohort 1 and Cohort 2**

1. Current use of any oral diabetes-specific medication.
2. Medical history of islet cell, kidney, and/or pancreas transplant.
3. Occurrence of two (2) or more severe, unexplained hypoglycemic events within six (6) months of enrollment.
4. Known causes of diabetes other than T1DM.
5. Diabetic complications such as:
    a. Renal dysfunction [macroalbuminuria defined as protein of 2+ or greater on dipstick, MDRD eGFR <60 mL/min/1.73m2]
    b. Proliferative retinopathy (active or untreated)
    c. Diabetic foot ulcers
    d. Amputations attributable to diabetes
    e. Severe peripheral neuropathy

6. Hemoglobin A1C (HbA1C) level of ≥10.0%.
7. Non-compliance with current anti-diabetic regimen.
8. Significant skin conditions in area(s) targeted for implantation. Examples include but are not limited to recurrent boils/furuncles, extensive surgery or scarring, or lipodystrophy.
9. Uncontrolled or untreated thyroid disease or adrenal insufficiency.
10. Current alcohol and/or drug (including marijuana) abuse or history of abuse within five (5) years of enrollment.
11. Positive urine drug screen for illicit substances of abuse at screening (Cohort 1) or screening and enrollment (Cohort 2). Note: A positive urine drug screen for marijuana does not automatically exclude a patient. If positive, the Investigator must determine if the extent of the subject's marijuana use meets the clinical definition of abuse.
12. Prior history of malignancy, except for:
    a. Basal cell carcinoma of the skin;
    b. Squamous cell carcinoma of the skin that has been recurrence free for ≥ five (5) years;
    c. Appropriately treated in situ carcinoma of the cervix.
13. Known allergies to portions of the cellular excipients used as cell preservation solution or the PEC-01 manufacturing process (i.e., bovine, porcine allergies).
14. History of severe asthma or chronic obstructive pulmonary disease (COPD).
15. Body mass index (BMI) ≥32 kg/m$^2$ or <18 kg/m$^2$ at screening
16. 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.
17. Active infection or known history of Hepatitis B or C.
18. Positive serology for human immunodeficiency virus (HIV) at screening.
19. Evidence of tuberculosis (TB) infection.
20. 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 (eGFR) <60 mL/min/1.73 $m^2$
e. Clinical lab value outside normal range, unless deemed as not clinically significant by the Investigator. Determination of clinical significance of a clinical lab value outside of normal range may also be evaluated by the Sponsor on a case-by-case basis.

21. Sustained hypertension defined as average systolic ≥160 mmHg or diastolic ≥90 mmHg at screening.
22. 12-lead electrocardiogram (ECG) findings demonstrating:
    a. QT interval (QTc) >450 msec for males or >470 msec for females at screening.
    b. Any other abnormality deemed clinically significant requiring further clinical evaluation by the Investigator.
23. History of unstable angina or Class 3 or 4 congestive heart failure (CHF), or any of the following 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 diagnosis or procedure.
24. History of coagulopathy.
25. Immunosuppressant therapy in the previous 30 days and/or requirements for chronic immunosuppressive therapy during the study as these may influence the expected action of the cells or graft. Individuals currently on immunosuppressant therapy may be considered on a case-by-case basis after consultation with the Sponsor.
26. Prescribed corticosteroid therapy above physiologic replacement doses in the previous 30 days.
27. 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.
28. Planned surgery in the general location of the implanted units [redacted]) at any time during study participation.
29. In the opinion of the Investigator, the subject is not suitable for the trial. This includes clinically significant medical and non-

medical conditions, and/or clinically-significant psychiatric disorders.

**Cohort 2 Only**

30. A detectable stimulated serum C-peptide at any time point during the Screening Period, defined as >0.2 ng/mL (>0.0667 nmol/L)

**Statistical Considerations**

**Sample Size**

**Cohort 1**

- The sample size in Cohort 1 was empirically derived, based on considerations and data accumulated from previously performed ViaCyte clinical trials. A sample size of up to 30 subjects should allow for adequate assessment of Cohort 1 study objectives.

**Cohort 2**

- A sample size of 40 subjects [redacted].
- If the minimal level of detection of 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 subjects enrolled into the study who received implantation of at least one sentinel and/or VC-01-DF unit on Study Day 1/Visit 3.
- The Safety Analysis Set (SAS) will include all subjects enrolled into the study and in whom an implant surgery was attempted, regardless if any sentinel or dose-finding units were actually implanted.

- For both the FAS and the SAS, treatment group is defined as the number of initially implanted sentinel units for Cohort 1, and the number of initially implanted VC-01-DF units for Cohort 2.

**Primary Analysis**

**Cohort 1**

- Histology results will be summarized by explant time point, anatomical location, and treatment group. The FAS will be used for these summaries.

**Cohort 2**

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. Cohort 2 subjects in the FAS will be used to analyze the primary efficacy endpoint (no Cohort 1 subjects will be included, as they have no MMTT data). The output from the ANCOVA will include the least squares mean (LSM) and standard error (SE) for each treatment group.

## Table 1. COHORT 1 SCHEDULE OF ASSESSMENTS[h]

| | V1 Screen | V2 Screen | V3 Enroll [i] | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 or ET | V12 FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assessments (Visit Windows)** | **Wk -2** (Within 2W of Day 1) | **Wk -1** (Within 1W of Day 1 | **Day 1** | **Day 2** (+1d) | **Wk 2** (+/-2d) | **Wk 4** (+/-3d) | **Wk 8** (+/-7d) | **Wk 12** (+/-7d) | **Wk 16** (+/-7d) | **Wk 20** (+/-7d) | **Wk 26** (+/-7d) | **Wk 27** (+/-3d) |
| Informed Consent | X | | | | | | | | | | | |
| Collect Contact Information | X | | | | | | | | | | | |
| Confirm Entry Criteria | X | X | X | | | | | | | | | |
| Demog/Med History/Prior Meds | X | | | | | | | | | | | |
| 12-lead ECG | X | | | | | | | | | | X | |
| Physical Exam (Complete) | X | | | | | | | | | | X | |
| Physical Exam (Abbreviated) | | | X | | 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 |
| Review Lifestyle Guidelines | X | X | X | X | X | X | X | X | X | X | X | |
| Confirm Implant Date w/ Sponsor | X | | | | | | | | | | | |
| Implantation Procedure | | | X | | | | | | | | | |
| Post-Implant Education/Therapies | | | X | | | | | | | | | |
| Explantation Procedure | | | | X (time-points as determined by Sponsor) | | | | | | | X | |
| Ultrasound - Safety Evaluation | | | | | | | X | | X | | X | |
| Ultrasound - Pre-Explant[a] | | | | X (time-points determined by explantations) | | | | | | | X | |
| Video and Photos[b] | | | X | X (time-points determined by explantations) | | | | | | | X | X |
| AE and Concomitant Medications | | X | X | X | X | X | X | X | X | X | X | X |
| Distribute Urine Sample Supplies for albumin/creatinine test (for next visit 1st morning void) | X | | | | | | | | | X | | |
| ICD for Follow-Up Study[c] | | | | | | | | | | | X | |

| | V1 Screen | V2 Screen | V3 Enroll [i] | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 or ET | V12 FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assessments (Visit Windows)** | **Wk -2** (Within 2W of Day 1) | **Wk -1** (Within 1W of Day 1 | **Day 1** | **Day 2** (+1d) | **Wk 2** (+/-2d) | **Wk 4** (+/-3d) | **Wk 8** (+/-7d) | **Wk 12** (+/-7d) | **Wk 16** (+/-7d) | **Wk 20** (+/-7d) | **Wk 26** (+/-7d) | **Wk 27** (+/-3d) |
| ***Laboratory Tests*** | | | | | | | | | | | | |
| Drug Screen | X | | | | | | | | | | | |
| HBsAg, HCV, HIV | X | | | | | | | | | | | |
| Hematology & Chemistry | X | X | X | | X | X | X | X | X | X | X | |
| eGFR | X | | | | | | | | | | | |
| HbA1c | X | | | | | | | | | | X | |
| Urine Pregnancy Test[d] | X | | X | | | | | | | | X | |
| Thyroid Stimulating Hormone | X | | | | | | | | | | | |
| Quantiferon TB | X | | | | | | | | | | | |
| Urinalysis | X | | | | | | | | | | | |
| Urine Albumin/Creatinine | | X | | | | | | | | | X | |
| Fasting Lipid Panel | X | | | | | | | | | | X | |
| Immune Panel<br>• HLA-PRA Class I & II Reactivity [e]<br>• HLA-PRA Class 1 & II ID[f]<br>T1DM Autoantibodies (GADA, IAA, IA2A and ZNT8) | | X | | | | X | | | X | | X | |
| Reserve Blood Samples[g] | | X | | | | X | | | X | | X | |

a. A pre-explant ultrasound is only required if the Surgeon is unable to identify the location of a sentinel unit planned for explantation thru palpation. If needed to locate unit, ultrasound may be done up to 3 days prior to explant.

b. Videos and/or photos are only required if requested by the Sponsor.

c. The informed consent process for the separate follow-up study is not a required procedure for this trial. It is included in this schedule as a reminder.

d. The urine pregnancy test is administered locally using the study-provided kit. Visit 3 results must be available before the implant procedure commences. Visit 11 or ET test should occur on the same day as the final explantation procedure.

e. The HLA-PRA and T1DM autoantibody samples may be collected at any time between Visit 1 and Visit 3, once the subject's study qualification is confirmed.

f. The HLA-PRA Class I and/or II Ab ID test is only required for each class that has a positive reactivity (e.g., >0%)

g. An additional reserve blood sample may be obtained at another time point at the request of the Sponsor.

h. With documented sponsor permission, on a case-by-case basis, certain protocol-required assessments may be performed remotely.

i. Pre-implant/explant assessments may be done up to 2 days prior to visit to accommodate logistical consideration depending on location of surgical center.

## Table 2. COHORT 2 SCHEDULE OF ASSESSMENTS[k]

| | V1 Screen | V2 Screen | V3[j] Enroll | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 or ET | V14 Follow- Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assessments (Visit Windows)** | **Wk -5** | **Wk -4** | **Day 1** | **Day 2** (+1d) | **Wk 2** (+/-2d) | **Wk 4** (+/-3d) | **Wk 8** (+/- 7d) | **Wk 12** (+/- 7d) | **Wk 16** (+/- 7d) | **Wk 20** (+/- 7d) | **Wk 26** **(+/- 7d)** | **Wk 39** (+/- 14d) | **Wk 52** (+/- 7d) | **Wk 53** (+/- 3d) |
| Informed Consent | X | | | | | | | | | | | | | |
| Collect Contact Information | X | | | | | | | | | | | | | |
| Confirm Entry Criteria | X | X | X | | | | | | | | | | | |
| Demog/Med History/Prior Meds | X | | | | | | | | | | | | | |
| 12-lead ECG | X | | | | | | | | | | X | | X | |
| Physical Exam (Complete) | X | | | | | | | | | | X | | X | |
| Physical Exam (Abbreviated) | | | X | | X | 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 |
| Review Lifestyle Guidelines | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Confirm Implant date w/Sponsor | X | | | | | | | | | | | | | |
| Dispense/Review CGM Data | | 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 | |
| Dispense/Review SMBG Supplies | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Implantation Procedure | | | X | | | | | | | | | | | |
| Post-Implant Education/Therapies | | | X | | | | | | | | | | | |
| Explantation Procedure | | | | X (time- points as determined by Sponsor) | | | | | | | | | X | |
| Ultrasound - Safety | | | | | | | 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 | X |
| AE and Concomitant Medications | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Distribute Urine Sample Supplies for albumin/creatinine test (for next visit 1st morning void) | X | | | | | | | | | X | | X | | |
| ICD for Follow-Up Study[c] | | | | | | | | | | | | | X | |

| | V1 Screen | V2 Screen | V3 [j] Enroll | V4 | V5 | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V13 or ET | V14 Follow- Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Assessments (Visit Windows)** | **Wk -5** | **Wk -4** | **Day 1** | **Day 2** (+1d) | **Wk 2** (+/-2d) | **Wk 4** (+/-3d) | **Wk 8** (+/- 7d) | **Wk 12** (+/- 7d) | **Wk 16** (+/- 7d) | **Wk 20** (+/- 7d) | **Wk 26** **(+/- 7d)** | **Wk 39** (+/- 14d) | **Wk 52** (+/- 7d) | **Wk 53** (+/- 3d) |
| ***Central Laboratory Tests or Study-Provided Testing Kits*** | | | | | | | | | | | | | | |
| Drug Screen[d] | X | | X | | | | | | | | | | | |
| HBsAg, HCV, HIV | X | | | | | | | | | | | | | |
| Hematology & Chemistry | X | X | X | | X | X | X | X | X | X | X | X | X | |
| eGFR | X | | | | | | | | | | | | | |
| HbA1c | X | | X | | | | | | X | | X | | X | |
| FSH[e] | X | | | | | | | | | | | | | |
| Urine Pregnancy Test[f] | X | | X | | | | | | | | | | X | |
| Thyroid Stimulating Hormone | X | | | | | | | | | | | | | |
| Quantiferon TB | X | | | | | | | | | | | | | |
| SOGCT C-peptide | X | | | | | | | | | | | | | |
| Ultrasensitive C-peptide[g] | | X | | | | | X | X | X | X | X | X | X | |
| 2-hr MMTT/C-peptide & Glucose | | | | | | | X | X | X | X | | X | | |
| 4-hr MMTT/C peptide & Glucose | | X | | | | | | | | | X | | X | |
| Urinalysis | X | | | | | | | | | | | | | |
| Urine Albumin/Creatinine | | X | | | | | | | | | X | | X | |
| Fasting Lipid Panel | X | | | | | | | | | | X | | X | |
| Immune Panel<br>• HLA-PRA Class I & II Reactivity<br>• HLA-PRA Class 1 & II ID[i]<br>• T1DM Autoantibodies (GADA, IAA, IA2A and ZNT8) | | X[h] | | | | X | | | X | | X | | X | |
| Inflammatory Biomarkers | | X | | | X | X | | X | | | X | | | |
| Reserve Blood Samples | | X | | | X | X | | X | | | X | | X | |

a. 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(s).

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. The informed consent process for the separate follow-up study is not a required procedure for this trial. It is included in this schedule as a reminder.

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. FSH testing only required for post-menopausal women.

f. The urine pregnancy test is administered locally with study-provided kit. Visit 3 results must be available before the implant procedure begins. Visit 13/ET test should occur on the same day as the final explant.

g. 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.

h. The HLA-PRA and T1DM autoantibody samples may be collected at any time between Visit 1 and Visit 3, once the subject's study qualification is confirmed.

i. The HLA-PRA Class I and/or II Ab ID reflex test is only required for each class that has a positive reactivity (e.g., >0%).

j. Pre-implant/explant assessments may be done up to 2 days prior to visit to accommodate logistical consideration depending on location of surgical center.

k. With documented sponsor permission, on a case-by-case basis, certain protocol-required assessments may be performed remotely.

# 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 International Conference on Harmonisation (ICH) Guidelines and the principles of Good Clinical Practice (GCP) as outlined in the Code of Federal Regulation (CFRs), as applicable.***

_____
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, the ICH Guidelines, and the principles of GCP as described in the CFRs 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.***

September 29, 2020

_____ _____
Howard Foyt, MD, PhD, FACP Date
Vice President, Clinical Development
ViaCyte Chief Medical Officer

# REVISION HISTORY

| Version Number | Version Date |
|---|---|
| 1.0 | 28 February 2019 (Original Protocol) |
| 2.0 | 16 June 2020 (Protocol Amendment 01) |
| 3.0 | 15 September 2020 (Protocol Amendment 02) |
| 4.0 | 29 September 2020 (Protocol Amendment 03) |

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADA | American Diabetes Association |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis of Covariance |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Curve |
| BCG | Bacille Calmette-Guerin |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| CFR | Code of Federal Regulations |
| CGM | Continuous Glucose Monitoring |
| CHF | Congestive Heart Failure |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CT | Computed Tomography |
| CTA | Clinical Trial Agreement |
| DSMB | Data Safety Monitoring Board |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| EDDS | Encaptra Drug Delivery System |
| EIU | Exposure in Utero |
| eGFR | Estimated Glomerular Filtration Rate |
| ET | Early Termination |
| FAS | Full Analysis Set |
| FBR | Foreign Body Response |
| FDA | Food and Drug Administration |
| FSH | Follicular Stimulating Hormone |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| HbA1C | Hemoglobin A1C |
| HBsAg | Hepatitis B Surface Antigen |
| HCV | Hepatitis C Virus |
| HDL | High-Density Lipoprotein |
| HE | Hypoglycemic Event |
| hESC | Human Embryonic Stem Cells |
| Hgb | Hemoglobin |
| HLA | Human Leukocyte Antigen |
| HIV | Human Immunodeficiency Virus |
| HU | Hypoglycemic Unawareness |
| IB | Investigators Brochure |
| ICD | Informed Consent Document |

| | |
|---|---|
| ID | Identification |
| ICH | International Conference on Harmonisation |
| IEQ | Islet Equivalent |
| IFU | Instructions for Use |
| ISO | International Organization for Standards |
| IUD | Intrauterine Device |
| IUS | Intrauterine hormone-releasing system |
| LAM | Lactation amenorrhea method |
| LDH | Lactate Dehydrogenase |
| LDL | Low-Density Lipoprotein |
| LSM | Least Squares Mean |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMTT | Mixed Meal Tolerance Test |
| MRI | Magnetic Resonance Imaging |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| PE | Physical Exam |
| PEC-01 | Pancreatic Endoderm Cells |
| PI | Principal Investigator |
| PPD | Purified Protein Derivative |
| PRA | Panel Reactive Antibody |
| PT | Preferred Term |
| QC | Quality Control |
| QTc | Corrected QT Interval |
| RBC | Red Blood Cell |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| 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 |
| SRM | Study Reference Manual |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T1DM | Type 1 Diabetes Mellitus |
| T2DM | Type 2 Diabetes Mellitus |
| TB | Tuberculosis |
| TEAE | Treatment-Emergent Adverse Event |
| ULN | Upper Limit Normal |
| VC-01 | VC-01 Combination Product |
| VLDL | Very Low-Density Lipoprotein |
| WBC | White Blood Cell |

# 1. INTRODUCTION

## 1.1. Background Information and Scientific Rationale

Diabetes mellitus, a life-threatening disease growing at an alarming rate, has nearly quadrupled in prevalence between 1980 and 2014 (World Health Organization, 2016). In 2017, the number of adults worldwide with diabetes was estimated to be 425 million, or approximately 8.8% of the world's adult population. This number is projected to increase to 629 million globally by 2045. In the United States alone, over 30 million adults are estimated to be living with diabetes, with as many as 11 million additional, undiagnosed diabetics (International Diabetes Federation, 2017). Of the people diagnosed with diabetes, approximately 5% to 10% have type 1 diabetes mellitus (T1DM) and require exogenous insulin injections every day to survive (You & Henneberg, 2016).

The hallmark of diabetes is elevated blood glucose levels. Over time, this chronic hyperglycemia frequently results in both microvascular (e.g., retinopathy, neuropathy, nephropathy) and macrovascular (e.g., atherosclerosis, cardiac disease) complications, which severely increase morbidity and mortality, and diminish the patient's quality of life. Annual economic costs attributable to diabetes in the United States include $176 billion for associated medical care and an additional $69 million related to time lost from work. Medical care costs for people with diabetes are 2.3 times higher than for those without diabetes (McEwen, et al., 2018). Care for people with diagnosed diabetes accounts for greater than one in five health care dollars. (American Diabetes Association, 2013).

Diabetes patients who require insulin treatment include all patients with T1DM, which is caused by loss of insulin-producing pancreatic beta cell mass, and 20-30% of patients with type 2 diabetes mellitus (T2DM), who require insulin as adjunctive therapy. Each year, more than 17,900 children and adolescents younger than age 20 years are diagnosed with T1DM in the US alone (National Center for Chronic Disease Prevention and Health Promotion, 2017).

There is no known way to prevent or cure T1DM. Treatment involves frequent, painful, and cumbersome blood glucose monitoring followed by insulin injection. This standard of care can be woefully inadequate. Subjects employing frequent self-monitoring (finger stick) blood glucose monitoring are able to maintain strict glycemic control within the American Diabetes Association (ADA)-specified optimal range less than 30% of the time. (Bode, Schwartz, Stubbs, & Block, 2005) The most intensive forms of insulin therapy involve the use of Continuous Glucose Monitoring (CGM) systems, finger stick blood glucose measurement with portable meters, and implanted insulin pumps. Yet even these technologically-advanced systems require significant patient management and cannot control glycemia perfectly. More recently, complex systems combining CGM technology and insulin pumps have been developed to function as an artificial pancreas. While the approach shows some promise, blood glucose control still remains sub-optimal relative to homeostatic euglycemia. Despite an increased use of technologies such as CGM and insulin pumps, only about 1 in 5 US patients with T1DM achieves optimal glycemic control (Foster, et al., 2019).

Importantly, insulin therapy also leads to periods of hypoglycemia. Patients using CGM may be hypoglycemic approximately 8% of each day, with a propensity for hypoglycemic events to occur

at night (Bode, Schwartz, Stubbs, & Block, 2005). In some cases, severe hypoglycemic events (SHE), e.g., those requiring the aid of another person to administer carbohydrates, glucagon, or other resuscitative assistance, can lead to seizures, unconsciousness, coma, and death. Importantly, a history of hypoglycemia can predispose patients to episodes of hypoglycemia unawareness (HU), which increases their risk of severe hypoglycemia and serious sequelae by at least 6-fold. (Seaquist, et al., 2013) Hypoglycemia, like hyperglycemia, should be avoided if possible.

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

ViaCyte's VC-01 combination product has the potential to overcome the disadvantages represented by pancreatic islet transplant, yet still provide homeostatic control of blood glucose levels that is difficult to achieve with CGM and insulin pumps alone. Clinical trials involving VC-01 were initiated in 2014, but results thus far have indicated that a robust foreign body response (FBR) occurs relative to the device component of the product, thus preventing long-term, viable engraftment of the product (Henry, et al., 2018). ViaCyte has now developed new configurations of the device that have been tested in Cohort 1 in this protocol to evaluate whether the FBR has been properly mitigated to allow for functional product engraftment. This protocol now includes an Efficacy Cohort 2, to evaluate the potential of the product to generate a response at higher doses that are expected to be therapeutic. Based on strong evidence of safety and histological response at sub-therapeutic doses, it is now prudent and necessary to evaluate the product for clinical efficacy.

## 1.2. Investigational Product

ViaCyte has developed the VC-01 combination product which is intended to control blood glucose in a more physiologic, sensitive, and homeostatic manner than the various forms of injectable insulin currently available. The VC-01 combination product is comprised of two distinct components: PEC-01 pancreatic endoderm cells derived hESC, and a durable, cell-impermeable, removable, macroencapsulation device known as the Encaptra® drug delivery system (EDDS). The VC-01 combination product will be either larger, dose-finding units (VC-01-DF) and/or small sentinel units implanted in an outpatient procedure.

The VC-01 combination product may be considered a pro-drug inasmuch as the pancreatic progenitor cell component matures to glucose-responsive, insulin-secreting cells only after implantation and further differentiation. The insulin-producing capability of VC-01 increases gradually; in nonclinical studies, the product reaches glucose-responsive activity capable of

regulating host glycemia at two to three months after implantation. Subcutaneously in rodents, the cells in the device differentiate into pancreatic endocrine cells, including those that express insulin and release it in a glucose-responsive fashion as well as cells expressing glucagon, somatostatin, pancreatic polypeptide, and ghrelin, similar to human islet tissue. Importantly, host vascularization accompanies graft maturation to provide a source for oxygen and other nutrients and a mechanism to deliver insulin and other graft-expressed hormones to the body.

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

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

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

- The Encaptra drug delivery system is macroporous, permitting free passage of oxygen, nutrients, proteins, and other macromolecules required to maintain the implanted cell viability and function.
- The Encaptra drug delivery system is impermeable to implanted and host cells. Thus, it permanently contains PEC-01 at a defined location, preventing them from distributing into host tissue.
- Once implanted, VC-01 can be monitored via ultrasound for evidence of device lumen expansion as an indicator of potentially unsafe, off-target cell growth.
- The Encaptra drug delivery system also prevents direct contact between the immune cells of the host and the cells of the graft. This physical barrier interferes with antigen presentation and disrupts the cell-mediated effector functions of the typical immune response. Similar physical barrier membrane systems have been shown to protect cells from allo- and auto-immune rejection (Lee, Hao, Savinov, Geron, Strongin, & Itkin-Ansari, 2009) as well as to protect against sensitization of the host. (Sorenby AK, Aug 15 2006:82(3)) In this way, immune-protection afforded by the device eliminates the need for, and the attendant safety risks of, chronic immunosuppression.
- Finally, in the event of loss of function, adverse reaction, or other potential safety concern, VC-01 units can be promptly removed in an out-patient procedure. The ability to explant the entire graft (and all cells contained in the graft) offers a unique safety advantage as compared to other cell therapies in which implanted cells cannot be retrieved.

## 1.3. Nonclinical Information

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

### 1.3.1. Evaluation of Safety of PEC-01 Cells

Nonclinical evaluation of the safety of PEC-01 includes characterization of the source hESC starting material, intermediate cell populations during PEC-01 drug substance manufacture, and the resulting differentiated pancreatic endoderm cell population. Evaluations of the hESC Master Cell Bank and Working Cell Bank were completed in accordance with applicable guidance documents. 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.

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

Nonclinical evaluations of the Encaptra drug delivery system include device biocompatibility studies and device integrity studies. Testing performed to date has demonstrated that the Encaptra device is capable of supporting survival, differentiation, and maturation of PEC-01 in vivo. Feasibility of utilizing the device to prevent biodistribution of implanted cells and to provide allogeneic immune protection against host cells has been demonstrated. Completed biocompatibility studies, conducted in accordance with Good Laboratory Practices (GLP), confirm that the device passes all biocompatibility tests. The Encaptra device is expected to significantly contribute to the safety profile of the VC-01 product by providing biocompatible and biostable encapsulation that prevents implanted cells from directly contacting host tissue.

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

Nonclinical evaluations of VC-01 safety and efficacy include [redacted] studies conducted in accordance with GLP. Completed studies demonstrated excellent tolerability of the graft with an absence of any related toxicity as well as an absence of tumor formation.

In these [redacted] GLP studies there was no evidence of teratoma formation. However, in a separate study when Encaptra devices were loaded with pure undifferentiated hESC (as a positive control) contents of the explants were principally comprised of chondrocytes and necrotic debris indicative of benign teratomas. These intentionally-generated teratomas were contained by the device. While hESC have not been observed in the PEC-01 cell population, all lots of cell product used to manufacture VC-01 for this clinical trial will be quality control (QC) tested for hESC contamination prior to product release, nevertheless, as a safety precaution. If a teratoma were to grow in a device, it would be detected via non-invasive imaging (see **Section 7.9**).

Studies conducted under GLP also characterize glucose-responsive human C-peptide secretion and the capacity of VC-01 to appropriately regulate host glycemia. Grafts examined histologically, confirm the absence of [redacted] within the device demonstrating the integrity, specifically the cell impermeability, of the encapsulating device.

Pharmacodynamic studies with VC-01 combination product demonstrate:

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

Nonclinical efficacy dose-range finding studies have been conducted. A principal conclusion from these studies is that the ultimate therapeutic capacity of the VC-01 combination product is not particularly dependent upon the number of cells administered; instead it is dictated by the volume capacity of the encapsulation device. For example, units of a given size (e.g., sentinel units) approximately the size of a fingernail and dose-finding units (VC-01-DF), approximately half the size of a credit card) ultimately achieve [redacted] loaded inside prior to implantation. The cells can proliferate to fill the device to capacity. Thus, it is expected that the dose capacity delivered is established more so by the number and size (capacity) of units implanted rather than the absolute number of cells delivered upon implant.

## 1.4. Clinical Information

The most current and comprehensive clinical information is available in the VC-01 IB. The details below provide a brief summary of the pertinent clinical information for VC-01.

### 1.4.1. Clinical Trials

Protocol VC01-101 is a Phase 1/2 first-in-human trial with the primary objective of establishing initial safety, tolerability, and efficacy of VC-01 in the T1DM patient population. A total of 19 subjects were implanted with VC-01 in this trial and all 19 subjects finished participation in the trial. There are no active subjects in the trial and it remains closed to new enrollment. ViaCyte intends to close-out the VC01-101 study, and through this VC01-103 study, continue to assess the safety, tolerability, engraftment (Phase 1/Cohort 1), and additionally, efficacy (Phase 2/Cohort 2) of VC-01. Upon confirmation of histological response in Cohort 1 subjects, demonstrating engraftment and the potential for clinical efficacy at a higher (therapeutic) dose, enrollment in the Efficacy Cohort 2 will be initiated.

Protocol VC01-201 is an ongoing Phase 2 observational, follow-up, safety study in subjects previously implanted with VC-01. Protocol VC01-201 enrolls subjects previously implanted with VC-01 combination product who have completed their treatment duration in the parent study. Thus far, no significant, long-term safety issues have been observed in subjects who were previously implanted with VC-01.

### 1.4.2. Potential Clinical Risks and Benefits

The most commonly occurring adverse events in subjects implanted with VC-01 to date are as follows: procedural pain, incision site pain, device dislocation and device breakage, vomiting and nausea, and implant site extravasation. Less commonly occurring adverse events are erythema,

implant site haemorrhage, implant site swelling, incision site haematoma, and paraesthesia. Laboratory data collected thus far suggest the adaptive immune system is neither compromised nor activated by treatment. To date, ultrasound imaging of implanted units indicates no significant expansion of the device lumens, correlating with a lack of any off-target or uncontrolled cellular growth. Overall, safety-related data collected to this point indicate VC-01 does not present undue risk to patients. For additional safety details, please refer to the VC-01 Investigator's Brochure.

While participating 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.

#### 1.4.2.1. Potential Risks

Some of the potential risks for study participation are hypothetical at this stage of VC-01 development. There are safety-related, strictly-defined discontinuation and explant rules noted in **Section 8.6**. Potential risks include, but are not limited to, the below items.

- There are inherent surgical risks during the implantation and explantation (removal) of the VC-01 units including pain, bleeding, hematoma, numbness, scarring, seroma, tenderness, redness, and infection.
- With any implant procedure, the possibility of migration or extrusion of the implant exists, along with the need for explantation. Steps will be taken to minimize the risks and to make the subject comfortable during the procedure with anesthetic and post-procedure analgesia.
- The use of anesthesia itself may cause side effects. The type(s) of anesthesia used during the implantation and explantation procedures will be determined by the Investigator or Surgeon. Side effects may include, but are not limited to:
  - Local anesthesia: Stinging and burning for a few seconds before numbing the skin and tissues. Other less likely side effects include nausea, vomiting, dizziness, drowsiness, local allergic reactions (e.g., redness, itching, and rash), low blood pressure, weakness, severe numbness or tingling, nerve damage, 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 implantation and vascularization of the implanted VC0-01 units there may be an increased risk for hypoglycemic events (HE).
  - In Cohort 1, the potential for HE risk is less likely to occur since subjects will only be implanted with sentinel units. At the projected dosing calculations, the total amount of sentinels allowed for implantation in Cohort 1 are not expected to provide a therapeutic level of endogenous insulin even if they remained implanted for the

maximum duration of six (6) months. These units will be explanted at various time points.

– In Cohort 2, although the risk for hypoglycemia from the 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 with local as needed. 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 captured. 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 7.12** - Blood Glucose Monitoring).

- There is a risk that VC-01 will have a shorter than expected duration of efficacy (if implanted with a therapeutic number of VC-01-DF units) or does not work as expected. [redacted]. Cell viability and product function of the VC-01 is expected to exceed the lifetime of animal models. The duration of exposure proposed for this clinical trial is approximately six (6) months for Cohort 1 and 12 months for Cohort 2.
- There are safety-related, strictly-defined stopping and explant rules noted in **Section 8.6**.
- There are risks that the implanted product may limit the subject's ability to be a candidate for future islet cell transplantation. This would occur if the subject were to unexpectedly become sensitized to VC-01 product, thus increasing the likelihood the subject's immune system would reject allogeneic donor material.
- 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. To date, no off-target growth in the clinic has been observed.
- There is a risk of immune reactions and inflammatory responses due to the implantation of the graft.
- There is a potential that the implanted units may rupture or break. [redacted] However, the device will not prevent penetration by a sharp object (e.g., insulin needle). If the device membrane were to be breached, the most likely effect would be a loss of efficacy.
- As human cells are being implanted, there is also a small risk that the subject could contract a disease or condition transmitted through the allogeneic cell line. This has not been observed in clinical trials to date.

#### 1.4.2.2. Potential Benefits

As VC-01 has not been studied beyond early clinical trials, there are no known benefits.

In Cohort 1, subjects participating in this group are not expected to derive any efficacy benefit from the sentinel units due to the sub-therapeutic islet equivalent (IEQ) dose. However, they may experience some degree of clinical benefit shown below. The sentinel units may be explanted at varying time points post-implant to assess graft cell viability, differentiation, vascularization, and host response.

In Cohort 2, with the planned number of dose-finding units (VC-01-DF), there is a higher likelihood of experiencing potential clinical benefits as noted below.

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

# 2. OBJECTIVES AND ENDPOINTS

This trial will test if VC-01 combination product can be implanted and maintained with safety, tolerability, and efficacy for up to Month 12/Week 52. During that period, VC-01 units are expected to vascularize adequately such that pancreatic progenitor cells may differentiate into mature beta cells capable of secreting insulin in response to serum glucose levels. The EDDS is anticipated to block direct antigen presentation of the graft and disrupt cell-mediated effector functions of both the auto- and allo-immune response. There are two Cohorts in this trial with the following study objectives:

## 2.1. Study Objectives

### 2.1.1. Cohort 1 Study Objectives

Primary Objective:

- Assess via histology the potential for functional engraftment of VC-01 combination product when implanted into subjects with T1DM.

Secondary Objectives:

- Assess via histology the host immune response to VC-01 combination product when implanted into subjects with T1DM.
- Evaluate the safety and tolerability of VC-01 combination product from implantation to Month 6/Week 26 or earlier if requested by the Sponsor.

### 2.1.2. Cohort 2 Study Objectives

Primary Objective:

- Evaluate the clinical efficacy of VC-01 combination product from implantation to Month 12/Week 52 or earlier if requested by the Sponsor.

Secondary Objectives:

- Further assess safety and tolerability of VC-01 combination product from implantation to Month 12/Week 52 or earlier if requested by the Sponsor.

Exploratory Objectives:

- Further assess via histology the potential for functional engraftment of VC-01 combination product when implanted into subjects with T1DM.
- Explore effects of weight, gender, BMI, or other potentially interacting factors on the responsiveness of the subjects to the experimental intervention.
- Optimize the recommended surgical implantation procedure, anatomical location, and peri- and post-operative care for VC-01.
- Further assess the effects of the host immune response to implanted VC-01 units.

## 2.2. Study Endpoints

The study endpoints for each Cohort are as follows:

### 2.2.1. Cohort 1 Study Endpoints

Primary Endpoint Measures:

- The percentage of viable graft cells at post-implant time points relative to pre-clinical models.
- The percentage of graft cells staining positive for markers of beta cells at post-implant time points relative to pre-clinical models.

Secondary Endpoint Measures:

- The qualitative assessment of the severity of the host immune response as rated at post-implant time points.
- The comprehensive safety profile of VC-01 implanted for up to six (6) months as measured by:
  - All reported AEs.
  - The incidence of subjects requiring a premature explant due to safety issues.
  - The incidence of off-target growth as evidenced by implanted VC-01 units via lumen ultrasound measurements, or by histological examination of explants.
  - The incidence of immune sensitization defined by presence of donor anti-HLA (human leukocyte antigen) antibodies absent prior to implant.

### 2.2.2. Cohort 2 Study Endpoints

Primary Endpoint Measure:

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

Secondary Endpoint Measures:

*Safety and Tolerability*

- Comprehensive profile of VC-01 combination product implanted for up to Month 12/Week 52 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) 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 8, 12, 16, 20, 39, and 52 in C-peptide $AUC_{0\text{-}2h}$ and change from baseline to Week 52 in C-peptide $AUC_{0\text{-}4h}$ following an MMTT.
- Change from baseline to Weeks 16, 20, 26, 39 and 52 in average daily insulin dose in the 7 days preceding the clinic visit.
- 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.
- Percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose from baseline to Weeks 16, 20, 26, 39, and 52.
- 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, >180 mg/dL and >250 mg/dL) as measured by each subject's CGM.
- Change from baseline to Weeks 16, 20, 26, 39 and 52 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 and >250 mg/dL) as measured by each subject's CGM.

*Exploratory*

- 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 clinical trial in subjects with T1DM. Two cohorts are planned for a total of up to 70 enrolled subjects (Cohort 1 – up to 30 subjects; Cohort 2 – up to 40 subjects).

Enrollment of Cohort 1 will occur prior to enrollment of Cohort 2, but Cohort 2 may advance prior to completion of all Cohort 1 subject activity.

All investigational units for both Cohorts are planned to be implanted [redacted] as deemed appropriate by the Investigator and/or Surgeon after consultation with the Sponsor. Documentation of the implant plan for a subject will be provided to the Investigator by the Sponsor. [redacted]

At the end of the treatment period, all remaining implanted units will be removed, and each subject will be presented with an ICD to participate in a separate, follow-up, non-interventional study (VC01-201 study). The primary purpose of the additional study is to ensure there are no long-term safety issues associated with previous implantation of VC-01 combination product.

## 3.1. Cohort 1

In Cohort 1, the Screening Period for each subject is expected to be approximately two (2) weeks in duration and comprised of two (2) study visits. Subjects qualifying for entry into Cohort 1 and who subsequently are implanted with VC-01 sentinel units may complete an additional ten (10) study visits over a period of approximately six (6) months. It is expected that a subject who completes the planned entire duration of the trial will therefore have a total of 12 study visits spanning approximately seven (7) months (including Screening, Treatment Period, and final Follow-up Visit). If the Sponsor has planned/scheduled an earlier explant (for non-safety reasons), this subject will also be considered as completing the study early (ET) with fewer study visits, as applicable.

Up to 30 enrolled subjects will receive subcutaneous implantation of up to ten (10) sentinel units only. The sentinel units may be explanted at varying time points post-implant to assess graft viability, differentiation, vascularization, and the host immune response.

After a minimum of three (3) subjects have been enrolled in Cohort 1 and have completed through Visit 6/Week 4, the Sponsor then has the ability to initiate enrollment of Cohort 2 and request the DSMB to review the completed 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.

## 3.2. Cohort 2

Upon confirmation of histological response in Cohort 1 subjects, demonstrating engraftment and the potential for clinical efficacy at a higher (therapeutic) dose, enrollment in the Efficacy Cohort 2 will be initiated.

In Cohort 2, the Screening Period for each subject is expected to be approximately five (5) weeks in duration and comprised of two (2) study visits. Subjects qualifying for entry into Cohort 2 and who subsequently are implanted with VC-01 sentinel units and/or dose-finding units (VC-01-DF) may complete an additional 12 visits over a period of approximately one (1) year. It is expected that a subject who completes the planned entire duration of the trial will therefore have a total of 14 study visits spanning approximately 13 ½ months (including Screening, Treatment Period, and final Follow-up Visit). If the Sponsor has planned/scheduled an earlier explant (for non-safety reasons), this subject will also be considered as completing the study early (ET) with fewer study visits, as applicable.

Up to 40 subjects will receive subcutaneous implantation of:

- Up to nine (9) VC-01-DF units, or;
- Up to 12 units total. Of the 12 units, no more than nine (9) will be dose-finding (VC-01-DF) and the remainder may be sentinel units. For example, if seven (7) VC-01-DF units are implanted in a subject, up to five (5) sentinels may be implanted.

The number of VC-01-DF 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 ongoing subjects to determine the optimal number of VC-01-DF units to implant in subsequent subjects. The Sponsor generally intends to implant the least number of VC-01-DF units required to provide the intended therapeutic benefit. Pre-clinical data suggest [redacted] VC-01-DF units may provide enough therapeutic benefit to allow a subject to discontinue exogenous insulin. However, if VC-01 does not function as robustly in humans as observed in pre-clinical models, then the number of VC-01-DF units required may be [redacted].

The sentinel units may be explanted at varying time points post-implant to assess graft cell viability, differentiation, vascularization, and host response. At the discretion of the Sponsor and after consultation with the Investigator, explantation of up to two (2) VC-01-DF units is allowed at any time post-implant without needing to withdraw the subject from the study.

## 3.3. Number of Patients and Sites

Up to 30 subjects in Cohort 1 and up to 40 subjects in Cohort 2 may be enrolled under this study at approximately ten (10) clinical sites.

## 3.4. Enrollment

All properly consented subjects will receive a unique, study subject identification (ID) number. Recruitment will occur at up to two (2) clinical sites in Cohort 1 and approximately ten (10) clinical sites in Cohort 2. Upon completion of screening, a subject is considered enrolled once an implant procedure is attempted. For Cohort 1, up to 30 subjects may be enrolled and implanted with up to ten (10) sentinel units. For Cohort 2, up to 40 subjects may be enrolled and implanted with up to 12 units total. Of the 12 units, no more than nine (9) will be dose-finding (VC-01-DF) and the remainder may be sentinel units.

Competitive enrollment of subjects is planned within each Cohort (e.g., subjects may be enrolled and implanted as frequently as possible by sites), but the Sponsor maintains the ability to alter the

pace of enrollment as necessary. Enrollment in Cohort 2 may advance prior to completion of Cohort 1. Any changes in the frequency and timing of enrollment will be communicated to sites by the Sponsor.

In both Cohorts, upon completion of Screening Visit 1 and after the Investigator has confirmed a subject has qualified for the study, sites must notify the Sponsor of the planned date of Visit 3 (Day 1– Implant Day). The Sponsor will confirm the acceptance of the planned implantation date in accordance with the Sponsor's manufacturing schedule for VC-01 units. Therefore, the rate of enrollment ultimately remains under the control of the Sponsor.

For Cohort 1 (Figure 1), the total duration of treatment (implantation of at least one unit) may be up to six (6) months for each subject, with the last sentinel unit explanted at Week 26 or earlier if requested by the Sponsor.

For Cohort 2 (Figure 2), the total duration of treatment (implantation of at least one unit) may be up to 12 months/Week 52 for each subject, with the last investigational unit(s) explanted at Week 52 or earlier if requested by the Sponsor.

Between Visit 3 (Day 1) and the final explant visit, investigational units may be explanted at varying time points as requested by the Sponsor.

**Figure 1 – Cohort 1**

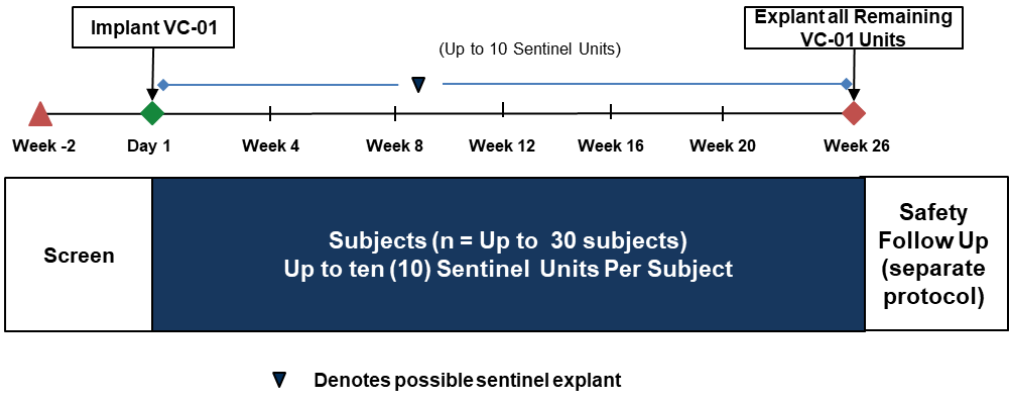
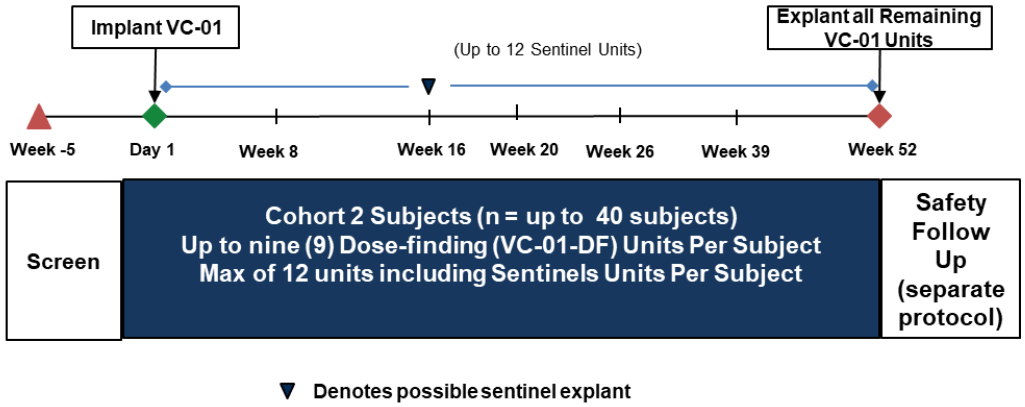



**Figure 2 – Cohort 2**



# 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 enrollment 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. Entry Criteria

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

### 4.1.1. Inclusion Criteria

**Cohort 1 and Cohort 2**

1. Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject has been informed of all aspects of the trial and agrees to participate in the trial
2. Men and non-pregnant women 18-65 years of age.
3. Diagnosis of T1DM for a minimum of three (3) years.
4. Stable, optimized diabetic regimen for at least 3 months.
5. Acceptable candidate for implantation and explantation procedures as assessed by Investigator
6. Willing and able to comply with scheduled visits, treatment plans, post-surgical care and restrictions, laboratory tests, and other study procedures.
7. All male subjects and female subjects of childbearing potential must practice highly-effective contraception, as described in Section 5.4.4, during the study and be willing and able to continue contraception until final explant.

**Cohort 2 Only**

8. Insulin dosage at screening <1 unit/kg/day (using previous seven days as average).
9. Willing to use a provided CGM System.
10. Willing and able to comply with daily entries on a study diary.

### 4.1.2. Exclusion Criteria

**Cohort 1 and Cohort 2**

1. Current use of any oral diabetes-specific medication.

2. Medical history of islet cell, kidney, and/or pancreas transplant.
3. Occurrence of two (2) or more severe, unexplained hypoglycemic events within six (6) months of enrollment.
4. Known causes of diabetes other than T1DM.
5. Diabetic complications such as:
    a. Renal dysfunction [macroalbuminuria defined as protein of 2+ or greater on dipstick, MDRD eGFR <60 mL/min/1.73m2]
    b. Proliferative retinopathy (active or untreated)
    c. Diabetic foot ulcers
    d. Amputations attributable to diabetes
    e. Severe peripheral neuropathy
6. Hemoglobin A1C (HbA1C) level of >10.0%.
7. Non-compliance with current anti-diabetic regimen.
8. Significant skin conditions in area(s) targeted for implantation. Examples include but are not limited to recurrent boils/furuncles, extensive surgery or scarring, or lipodystrophy.
9. Uncontrolled or untreated thyroid disease or adrenal insufficiency.
10. Current alcohol and/or drug (including marijuana) <u>abuse</u> or history of abuse within five (5) years of enrollment.
11. Positive urine drug screen for illicit substances of abuse at screening (Cohort 1) or screening and enrollment (Cohort 2). Note: A positive urine drug screen for marijuana does not automatically exclude a patient. If positive, the Investigator must determine if the extent of the subject's marijuana use meets the clinical definition of abuse.
12. Prior history of malignancy, except for:
    a. Basal cell carcinoma of the skin;
    b. Squamous cell carcinoma of the skin that has been recurrence free for ≥ five (5) years;
    c. Appropriately treated in situ carcinoma of the cervix.
13. Known allergies to portions of the cellular excipients used as cell preservation solution or the PEC-01 manufacturing process (i.e., bovine, porcine allergies).
14. History of severe asthma or chronic obstructive pulmonary disease (COPD).
15. Body mass index (BMI) ≥32 kg/m2 or <18 kg/m2 at screening
16. 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.
17. Active infection or known history of Hepatitis B or C.
18. Positive serology for human immunodeficiency virus (HIV) at screening.
19. Evidence of tuberculosis (TB) infection.

20. 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 (eGFR) <60 mL/min/1.73 m2
    e. Clinical lab value outside normal range, unless deemed as not clinically significant by the Investigator. Determination of clinical significance of a clinical lab value outside of normal range may also be evaluated by the Sponsor on a case-by-case basis.
21. Sustained hypertension defined as average systolic ≥160 mmHg or diastolic ≥90 mmHg at screening.
22. 12-lead electrocardiogram (ECG) findings demonstrating:
    a. QT interval (QTc) >450 msec for males or >470 msec for females at screening.
    b. Any other abnormality deemed clinically significant requiring further clinical evaluation by the Investigator.
23. History of unstable angina or Class 3 or 4 congestive heart failure (CHF), or any of the following 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 diagnosis or procedure.
24. History of coagulopathy.
25. Immunosuppressant therapy in the previous 30 days and/or requirements for chronic immunosuppressive therapy during the study as these may influence the expected action of the cells or graft. Individuals currently on immunosuppressant therapy may be considered on a case-by-case basis after consultation with the Sponsor.
26. Prescribed corticosteroid therapy above physiologic replacement doses in the previous 30 days.
27. 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.
28. Planned surgery in the general location of the implanted units [redacted] at any time during study participation.
29. In the opinion of the Investigator, the subject is not suitable for the trial. This includes clinically significant medical and non-medical conditions, and/or clinically-significant psychiatric disorders.

**Cohort 2 Only**

30. A detectable stimulated serum C-peptide at any time point during the Screening Period, defined as >0.2 ng/mL (>0.0667 nmol/L).

# 5. INVESTIGATIONAL PRODUCT & STUDY INTERVENTIONS

## 5.1. VC-01™ Combination Product Description

VC-01 Combination Product is comprised of two distinct components: (1) PEC-01 pancreatic endoderm cells derived from hESC loaded into (2) a durable, immune-protective, and removable Encaptra Drug Delivery System (EDDS) designed to deliver and macro-encapsulate the cells at the local implant site. Each sentinel unit is approximately the size of a fingernail, and the larger, dose-finding (VC-01-DF) unit is roughly half the size of a business card. Sites are not blinded and will be aware of which units are implanted. .

During the first three (3) to six (6) months following implantation, the VC-01 units are expected to vascularize adequately, and the PEC-01 cells are expected to differentiate into mature glucose-responsive cells, capable of secreting insulin and other hormones as required to regulate serum glucose concentrations.

[redacted]

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

### 5.1.1. Manufacturing, Formulation, Packaging, and Labeling

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

Tiered Master and Working Cell Banks of the [redacted] line have been qualified. The cell line identity is assured via quality processes, batch records, and labeling. [redacted]

Upon the receipt and confirmation of a scheduled implantation procedure for a subject, the ViaCyte Study Team will then initiate a manufacturing build request to ensure the proper quantity of each type of unit (either VC-01-DF or sentinel) is made available to the site. [redacted] Additional details regarding the packaging, labeling, and transport of the investigational units are provided to the site during study start-up activities.

### 5.1.2. Transport of Investigational Product to Site

ViaCyte ships investigational product to each site's designated receipt facility. 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, all environmental shippers and temperature loggers are to be returned as instructed by the Sponsor.

Further details may be outlined in the Study Reference Manual.

### 5.1.3. Product Storage, Stability, and Accountability

The shelf-life of the product is qualified for [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]. 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 containers so an appropriate evaluation can be done.

The Investigator is responsible for the accountability of all used and unused investigational product. Please refer to the Study Reference Manual for additional details.

### 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-01. 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-01 are implanted, depending on the Cohort.

In Cohort 1, each subject can be implanted with up to ten (10) sentinel units.

In Cohort 2, each subject can be implanted with up to 12 VC-01 units total. Of the 12 units, no more than nine (9) will be dose-finding (VC-01-DF) and the remainder may be sentinel units. For example, if the maximum of nine (9) VC-01-DF units are scheduled for implant, only three (3) sentinel units may be included in the implantation plan. Or if only seven (7) VC-01-DF units are planned, then five (5) sentinel units can be implanted.

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 7.2** and the Instructions for Use (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-01 are not permitted. However, in Cohort 2, at the discretion of the Sponsor and after consultation with the Investigator, explantation of up to two (2) VC-01-DF units 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-01-DF units and all remaining sentinels explanted.

Since VC-01 is implanted into each subject, assessment of subject compliance with the investigational product does not apply. If, however, the expected number of units is not implanted into a subject, this needs to be recorded in the subject's source documentation.

#### 5.1.4.1 Cohort 1

In Cohort 1, a subject implanted with ten (10) sentinels has the potential to achieve a total dose of [redacted] after six (6) months (**Table 3**). Given [redacted] estimated for subjects implanted with the maximum number of sentinels allowed in this study, along with the likelihood that multiple sentinels will be explanted prior to Visit 11 (Week 26), it is not expected that any subject in Cohort 1 will receive therapeutic benefit from participation in this trial.

**Table 3. VC-01 Sentinel Dosing Projections (75 kg Human)**

| Device (Quantity) | 6-Months Post-Implant (Cell Output) | |
|---|---|---|
| | IEQ | Per Kilogram IEQ |
| VC-01-20 (1) | [redacted] | [redacted] |
| VC-01-20 (2) | [redacted] | [redacted] |
| VC-01-20 (6) | [redacted] | [redacted] |
| VC-01-20 (10) | [redacted] | [redacted] |

#### 5.1.4.1 Cohort 2

In Cohort 2, however, the VC-01-DF units are intended to provide a measurable, therapeutic benefit to enrolled subjects. VC-01-DF units contain approximately [redacted] cells at the time of

formulation, but at the time of implantation the IEQ are negligible. After implant, a portion of the administered cells survive the acute engraftment period (defined as the first approximately 4 weeks) and surviving graft cells further differentiation to endocrine cells and progressively increase in beta cell content over a period of several months.

If the product were to perform equivalently in human subjects as it does in the preclinical model [redacted] based on linear extrapolation of volumetric capacity from the corresponding sentinel to the VC-01-DF, each VC-01-DF has the capacity to deliver approximately [redacted] after six (6) months of *in vivo* maturation.

It is anticipated that approximately 200,000 IEQ (Meier, Butler, & Saisho, 2008), equivalent to approximately 20% of normal beta cell mass, are required to achieve insulin independence. Thus, a subject implanted with [redacted] (**Table 4**).

**Table 4. VC-01-DF Dosing Projections (75 kg Human)**

| Device Type and (Quantity) | At Implant (Cell Input) | | Fold Safety Factor Based on Cell Input | 6 Months (Cell Output) | |
|---|---|---|---|---|---|
| | PEC-01 cells ($x10^7$) | PEC-01 cells ($10^6$/kg) | | IEQ | Per kg IEQ |
| VC-01-DF (1) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| VC-01-DF (2) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| VC-01-DF (9) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Pre-clinical data suggest as few as [redacted] VC-01-DF units, if functioning at 100% of preclinical models, may provide enough therapeutic benefit to allow a subject to discontinue exogenous insulin. However, if VC-01 does not function as robustly in humans as observed in pre-clinical models, then the number of VC 01-DF units required may be up to a maximum [redacted]. If more than [redacted] VC-01-DF units are 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.

## 5.2. Exogenous Insulin and Blood Glucose Monitoring

Post-implant, subjects must be instructed not to inject insulin in areas near implantation sites to avoid accidentally rupturing the device membrane.

Likewise, the method and frequency of blood glucose monitoring of enrolled subjects are to be managed at the discretion of the Investigator in accordance with local standard of care to maintain glycemic control.

### 5.2.1. Cohort 1

As no therapeutic benefit is expected from the VC-01 sentinel units implanted in Cohort 1, subjects will remain on exogenous insulin therapy as appropriate to maintain blood glucose control throughout the duration of the study. The dose, brand, method of delivery (e.g., pump or multiple daily injections), and types (e.g., short- or long-acting) of insulin may be modified over the course of the study at the discretion of the Investigator in accordance with the local standard of care. All changes in insulin therapy should be documented in the subject's source document and case report form (CRF).

### 5.2.2. Cohort 2

Subjects in Cohort 2 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 first consulting with the Principal Investigator, the Sponsor and Medical Monitor. Subjects are required to log their insulin doses every day on the study diary throughout participation in the trial (**Section 7.13**).

## 5.3. Concomitant Medications/Treatments

The Surgeon or Investigator, in consultation with the Sponsor, may prescribe additional concomitant medication or treatments. Examples of some potential concomitant treatments include but are not limited to:

[redacted]

Any additional therapies for pre-existing and new medical conditions, and prophylaxis use, 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 engraftment of VC-01. 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 5.2**.

## 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** and **Table 2**, for Cohort 1 and Cohort 2 respectively. It is advisable that sites remind subjects of these restrictions several days prior to visits. Sites must reinforce these restrictions 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 eight (8) hours prior to any blood sample collection for clinical lab tests unless otherwise indicated.

Subjects not fasting before a scheduled clinic visit requiring a fasted state will be required to return in a fasted state to complete lab sample collection within the protocol visit window.

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

### 5.4.2. 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, are acceptable. Subjects may be asked to provide information on their normal exercise routine (collected at baseline and updated throughout the study). This is to assess how activity levels may impact the healing and engraftment process.

### 5.4.3. 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.

### 5.4.4. Contraception

Men and non-pregnant women will be allowed into the study.

All male subjects and female subjects of childbearing potential and that are sexually active must be willing to practice effective contraception consistently and correctly through the entire study period until final explant procedure (Cohort 1: Visit 11 or Early Termination; Cohort 2: Visit 13 or Early Termination).

The subject will select **one** of the most appropriate methods of contraception from a permitted list (see below). The Investigator or designee 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 or designee will instruct the subject to call immediately if the selected birth control method is discontinued or if a pregnancy is known or suspected for either the subject or subject's partner impregnated by subject. Subject must agree to consistently and correctly use **one** of the following acceptable (and considered highly-effective methods):

#### 5.4.4.1. Acceptable Methods of Contraception

- Combined hormonal contraception (estrogen and progestogen containing) associated with inhibition of ovulation (oral, intravaginal, or transdermal).
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine Device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Vasectomy (with medical record of surgical success [sperm analysis])
- Bilateral tubal occlusion or ligation
- Postmenopausal (at least one complete year without menstrual bleeding in absence of any surgery or medical condition that may cause bleeding to artificially stop)
- Total hysterectomy or bilateral oophorectomy
- Commitment to 100% abstinence (defined as refraining from heterosexual intercourse during the entire period of the study). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
- *The double-barrier method (diaphragm with spermicide and a condom; cervical cap and a condom; or contraceptive sponge and a condom). ***Note:** The double-barrier method is not as effective as the other options listed above. In order to be acceptable for this study, the subject must be committed to use the double-barrier method every time as described in the product instructions.

If one of the highly-effective methods listed above is initiated (or procedure performed i.e., vasectomy or bilateral tubal occlusion/ligation) less than 4 weeks before implant day (Visit 3) or during the study period, subject must also agree to use a double barrier method (diaphragm with spermicide and a latex condom; cervical cap and a latex condom; or contraceptive sponge and a latex condom) until the efficacy of the initial method is known to work or be effective. This also applies if the subject switches methods or product brands to ensure the new method is known to work or be effective.

#### 5.4.4.2. Non-Acceptable Methods of Contraception

Birth control methods **not considered acceptable** are:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Condoms only
- Spermicides only
- Lactation amenorrhea method (LAM)

The PI (or designee) must do an assessment of the subject's knowledge of the correct use of contraceptive method during the screening period. Further, at every study visit, a re-assessment should be made to confirm the current contraception method and their continued correct usage. These reviews should be documented within the subject's source record at each visit.

### 5.4.5. Other Restrictions

In Cohort 2, 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 engraftment or safety of VC-01. If required for safety reporting, the information will be communicated to sites as quickly as possible to inform the subjects and/or Ethics Committee.

## 6. STUDY SCHEDULE

The visit schedule for study subjects is outlined in the Schedule of Assessments, **Table 1** (Cohort 1) and **Table 2** (Cohort 2). If needed, procedures may occur separate days, though they should be done within the defined protocol window. Some assessments are only required for Cohort 2 and are indicated as such. 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 (performed after the subject has rested for at least 10 minutes in a supine position)
2. Vital signs (sitting blood pressure, pulse, and temperature)
3. Blood and urine samples
4. Cohort 2 Only: Simplified Oral Glucose Challenge Test (SOGCT) (Visit 1 only) or Mixed Meal Tolerance Test (MMTT) (Visits 2 – 13) . For visits requiring both an MMTT and an explant procedure, the site may perform the MMTT within five (5) days prior to the explant procedure.
5. Ultrasound Monitoring

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.

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

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

## 6.1. Screening Visit 1 (Cohort 1: Week -2 to Week -1; Cohort 2: Week -5 to Week -4)

The Screening Period is comprised of two visits: Visit 1 and Visit 2. For Cohort 1, the Screening Period can be performed over approximately two (2) weeks, whereas Cohort 2 can be over approximately five (5) weeks. It is permissible for Screening Visit 1 procedures to occur over multiple days. Subjects must be fasted for this visit. The following procedures will be completed:

- Obtain informed consent.

  ***Note***: It is acceptable for consent to be obtained prior to the Screening Visit 1.
- Obtain a 12-lead ECG (performed after the subject has rested for at least 10 minutes in a supine position)
- Obtain weight and vitals.
- Measure height
- Collect demography, medical history (including smoking status, alcohol and/or marijuana frequency, and hormonal status), prior medications (within 30 days), and concomitant medications.
- Obtain contact information for the subject's health care provider and/or family members in order to reach subject if other contact methods are unsuccessful.
- Perform a complete physical exam (PE).
- Obtain all laboratory samples per the Schedule of Assessments.
- Provide subject with appropriate supplies to take home in preparation for urine sample to be taken on the morning of Screening Visit 2.
- Review eligibility criteria to assess suitability for the trial.
- Review Lifestyle Guidelines.
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.

- Confirm Implant date with the Sponsor.
- Cohort 2 only: Conduct the SOGCT.

Upon confirmation of Visit 1 screening eligibility assessments and lab results, contact the Sponsor to schedule provisioning of VC-01 for an implant date.

## 6.2. Screening Visit 2 (Cohort 1: Week -1; Cohort 2: Week -4)

Subjects deemed to have met eligibility criteria after completion of Screening Visit 1 may return for Screening Visit 2. Visit 2 may be accelerated to occur sooner than indicated on Schedule of Assessments if results from Visit 1 have already been obtained and validate continued screening of the subject. Subjects must be fasted for this visit. The following procedures will be completed:

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

  ***Note***: The HLA-panel reactive antibody (PRA) and T1DM autoantibody samples may be collected at any time between Visit 1 and Visit 3, once the subject's study qualification is confirmed (**Section 7.17.3**).
- Cohort 2 Only:
  - Perform 4-hr MMTT. This is the baseline MMTT for efficacy evaluation.
  - Ultrasensitive C-peptide samples obtained in conjunction with 4-hr MMTT pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.
  - Dispense Continuous Glucose Monitor (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 study requires daily compliance with entries between Visit 2 and Visit 3.**
- Assess AEs and concomitant medications.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.

- Contact the Sponsor to report any schedule changes or updates to the implant date.

The expected duration of the Screening Period is approximately two (2) weeks total for Cohort 1 and approximately five (5) weeks total for Cohort 2.

If the Enrollment Visit 3 (Day 1) is scheduled to occur beyond four (4) weeks (>28 days) for Cohort 1 or beyond six (6) weeks (>42 days) for Cohort 2 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 in Cohort 1 to less than two (2) weeks total if all visit procedures and results are completed and confirm the subject's eligibility for the trial. For Cohort 2, 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. Depending on the location of the surgical center, some of these assessments may be performed up to two (2) days prior to implantation day to accommodate logistical considerations. At this visit, the following procedures will be completed:

- Obtain weight and vitals.
- Ensure eligibility criteria continue to be met.
- Perform an abbreviated PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Perform urine pregnancy test. Results must be available before the implant procedure commences.
- Assess AEs and Concomitant Medications.
- Cohort 2 only:
  - Perform urine drug screen prior to implant procedure.
  - Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.
- Prepare subject for implantation.
- Implant VC-01 units.

- Obtain video and/or photos of the implantation procedure if requested by the Sponsor (see **Section 7.7**).
- Dress the subject with the appropriate post-operative garments.
- Assess subject for AEs during post-op period through discharge.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 6.4. Visit 4 (Day 2)

There is a +1-day window for this visit. However, if the procedure is performed on a Friday, Visit 4 can be conducted on the following Monday. Subjects do *not* need to fast for this visit. The following procedures will be completed:

- Obtain weight and vitals.
- Perform a targeted PE focusing on the implantation site(s).
- Assess AEs and concomitant medications.
- Cohort 2 only:
  - Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.

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

- If unable to locate a unit via palpation, perform an 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).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 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 and vitals.
- Perform an abbreviated PE.
- Obtain laboratory samples per the Schedule of Assessments.
- Assess AEs and concomitant medications.
- Cohort 2 only:
  - Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.

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

- If unable to locate a unit via palpation, perform an 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).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 6.6. Visit 6 (Week 4)

There is a ±3-day window for this visit. Subjects must be fasted for this visit. The following procedures will be completed:

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

- Assess AEs and concomitant medications.
- Cohort 2 only:
  - Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.

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

- If unable to locate a unit via palpation, perform an 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).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 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 and vitals.
- Perform an abbreviated PE.
- Obtain laboratory samples per the Schedule of Assessments.
- Assess AEs and concomitant medications.
- Cohort 2 only:
  - Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
  - Perform 2-hr MMTT.
  - Ultrasensitive C-peptide samples obtained in conjunction with 2-hr MMTT pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.
- Review Lifestyle Guidelines

  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.
- Perform the *safety* ultrasound assessment of all remaining implanted sentinels.

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

- If unable to locate a unit via palpation, perform an 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).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 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 and vitals.
- Perform an abbreviated PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Assess AEs and concomitant medications.
- Cohort 2 only:
  - Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
  - Perform 2-hr MMTT.
  - Ultrasensitive C-peptide samples obtained in conjunction with 2-hr MMTT pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.

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

- If unable to locate a unit via palpation, perform an 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).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 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 and vitals.
- Perform an abbreviated PE.
- Obtain laboratory samples per the Schedule of Assessments.
- Assess AEs and concomitant medications.
- Cohort 2 only:
  - Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
  - Perform 2-hr MMTT.
  - Ultrasensitive C-peptide samples obtained in conjunction with 2-hr MMTT pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.
- Perform the *safety* ultrasound assessment of all remaining implanted sentinels.

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

- If unable to locate a unit via palpation, perform an 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).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 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 and vitals.
- Perform an abbreviated PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Assess AEs and concomitant medications.
- Cohort 2 only:
  - Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
  - Perform 2-hr MMTT.
  - Ultrasensitive C-peptide samples obtained in conjunction with 2-hr MMTT pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.
- Provide subject with appropriate supplies to take home in preparation for urine sample to be taken on the morning of Visit 11 (Week 26).

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

- If unable to locate a unit via palpation, perform an 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).
- Dress the subject with the appropriate post-operative garments, if applicable.

- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 6.11. Visit 11

### 6.11.1. Cohort 1 – Visit 11 (Week 26) / Study Completion 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 prematurely from the study at any time, the procedures outlined in Visit 11 should be performed. The following procedures will be completed:

- Obtain 12-lead ECG (performed after the subject has rested for at least 10 minutes in a supine position)
- Obtain weight and vitals.
- Perform a complete PE.
- Obtain all laboratory samples per the Schedule of Assessments, including urine sample from subject's first morning void.
- Perform urine pregnancy test. Results must be available before the final explant procedure commences.
- Assess AEs and concomitant medications.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.
- Perform the *safety* ultrasound assessment of all remaining implanted sentinels.
- If unable to locate a unit via palpation, perform an ultrasound to locate the unit(s) planned for explantation (up to 3 days prior).
- Prepare subject for explantation procedure:
  - Explant all remaining sentinel units.
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.

- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.
- Review participation requirements for the separate, long-term, follow-up study (the ICD process for the follow-up study can be initiated).
- Remind subject of the follow-up Visit 12.

### 6.11.2. Cohort 2 – Visit 11 (Week 26)

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

- Obtain 12-lead ECG.
- Obtain weight and vitals.
- Perform a complete PE.
- Obtain all laboratory samples per the Schedule of Assessments, including urine sample from subject's first morning void.
- Assess AEs and concomitant medications.
- Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
- Perform 4-hr MMTT.
- Ultrasensitive C-peptide samples obtained in conjunction with 4-hr MMTT pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.
- Perform the *safety* ultrasound assessment of all remaining implanted units.

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

- If unable to locate a unit via palpation, perform an 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).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.

- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 6.12. Visit 12

### 6.12.1. Cohort 1 - Visit 12 (Follow-up Week 27)

There is a ±3-day window for this visit. All subjects in Cohort 1, regardless of whether or not they completed or early terminated from the trial, complete this visit to follow-up on unresolved AEs and the post-explantation experience. Cohort 1 Subjects do *not* need to fast for this visit. The following procedures will be completed:

- Obtain weight and vitals.
- Perform a targeted PE of all explantation site(s).
- Assess AEs and concomitant medications.
- Review Lifestyle Guidelines
  - Review dietary, alcohol/tobacco/caffeine and other guidelines as part of T1DM SOC as described under **Section 5.4.5** (as applicable for final follow-up visit).
- Obtain photos of the explantation sites (if requested by Sponsor).
- Obtain ICD for follow-up study (if not completed at Visit 11).

### 6.12.2. Cohort 2 - Visit 12 (Week 39)

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

- Obtain weight and vitals.
- Perform an abbreviated PE.
- Obtain all laboratory samples per the Schedule of Assessments.
- Assess AEs and concomitant medications.
- Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
- Perform 2-hr MMTT.
- Ultrasensitive C-peptide samples obtained in conjunction with 2-hr MMTT pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.

- Provide subject with appropriate supplies to take home in preparation for urine sample to be taken on the morning of Visit 13 (Week 52).

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

- If unable to locate a unit via palpation, perform an 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).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.

## 6.13. Cohort 2 - Visit 13 / Study Completion or Early Termination (Week 52)

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

If a subject withdraws or is discontinued prematurely from the study at any time, the procedures outlined in Visit 11 should be performed. The following procedures will be completed:

- Obtain 12-lead ECG.
- Obtain weight and vitals.
- Perform a complete PE.
- Obtain all laboratory samples per the Schedule of Assessments, including urine sample from subject's first morning void.
- Perform urine pregnancy test. Results must be available before the final explant procedure commences.
- Assess AEs and concomitant medications.
- Review Lifestyle Guidelines
  - Review dietary restrictions, physical activity, alcohol/tobacco/caffeine and other guidelines as described under **Section 5.4.5**.
  - Assess the subject's knowledge of the correct use of contraceptive method, confirm the current contraception method, and the subject's continued correct usage.
- Collect and review CGM, SMBG, and diary data and verify that subject has demonstrated compliance with diary entries. Dispense additional supplies.
- Perform 4-hr MMTT.

- Ultrasensitive C-peptide samples obtained in conjunction with 4-hr MMTT pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.
- Perform the *safety* ultrasound assessment of all remaining implanted VC-01 units.
- If unable to locate a unit via palpation, perform an ultrasound to locate the unit(s) planned for explantation (up to 3 days prior).
- Prepare subject for explantation procedure:
  - Explant all remaining VC-01 units.
- Obtain video and/or photos of the explantation procedure (if requested by Sponsor).
- Dress the subject with the appropriate post-operative garments, if applicable.
- Subjects may be in post-op up to 4 hours but can be discharged sooner at the discretion of the Surgeon.
- Remind subject of post-op instructions and to limit significant physical activity to ensure optimal healing at implantation sites.
- Review participation requirements for the separate, long-term, follow-up study (the ICD process for the follow-up study can be initiated).
- Remind subject of the follow-up Visit 14.

## 6.14. Cohort 2 - Visit 14 (Follow-up Week 53)

There is a ±3-day window for this visit. All subjects in Cohort 2, regardless of whether or not they completed or early terminated from the trial, complete this visit to follow-up on unresolved AEs and the post-explantation experience. Subjects do *not* need to fast for this visit. The following procedures will be completed:

- Obtain weight and vitals.
- Perform a targeted PE of all explantation site(s).
- Assess AEs and concomitant medications.
- Review Lifestyle Guidelines
  - Review dietary, alcohol/tobacco/caffeine and other guidelines as part of T1DM SOC as described under **Section 5.4.5** (as applicable for final follow-up visit).
- Obtain photos of the explantation sites (if requested by Sponsor).
- Obtain ICD for follow-up study (if not completed at Visit 13) if the subject chooses to enter

## 6.15. Unplanned/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:

- Adverse event follow-up.

- Abnormal laboratory test follow-up.
- 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-01 unit.
- Obtain video and/or photos of an explantation procedure.
- Review of blood sugar values with possible exogenous insulin dose adjustments.
- Perform an SOGCT or MMTT.

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).

# 7. STUDY ASSESSMENTS

Every effort should be made to ensure protocol-required tests and procedures are completed as described. 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 for the protocol deviation 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. Also, with documented sponsor permission, on a case-by-case basis, certain protocol-required assessments may be performed remotely (i.e., adverse event reports or updated concomitant medications).

## 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. Refer to applicable Schedule of Assessments for when specific PEs are to be performed.

1. A **complete** PE evaluates the following body systems: general appearance, skin, head/eyes/ears/nose/throat, heart, lungs, abdomen, extremities, neurological, back/spinal/flank area, and lymph nodes.
2. An **abbreviated** PE assesses the heart, lungs, abdomen, extremities, and skin (including implantation and/or explantation site[s]).
3. A **targeted** PE focuses on the evaluation of the healing status at the implantation and/or explantation sites.

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.

### 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 applicable Schedule of Assessments for either Cohort 1 or Cohort 2. Caffeine and nicotine products are prohibited for at least 30 minutes prior to ECG. 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 with the subject's source records.

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.

1. Caffeine and nicotine products are prohibited for at least 30 minutes prior to obtaining measurements.
2. Subjects should be seated in a chair with their backs supported, feet flat on the floor, and arms bared and supported at heart level.
3. The appropriate cuff size must be used to ensure accurate measurement and used consistently throughout the study.
4. Readings should be done on the same arm at each visit, preferably the non-dominant arm.

5. Measurement should begin after at least five minutes of rest.
6. 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) – Cohort 2 only

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. The MMTT may be rescheduled within the visit window if needed. 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 – Cohort 2 Only

The 4-hour MMTT is conducted only in Cohort 2 during Visit 2 (Week -4), Visit 11 (Week 26), and Visit 13 (Week 52 / 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 – Cohort 2 Only

The 2-hour MMTT is conducted only in Cohort 2 during Visit 7 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), and Visit 12 (Week 39). 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) – Cohort 2 Only

All subjects in Cohort 2 complete the SOGCT at Visit 1 to confirm a stimulated C-peptide level >0.2 ng/mL (>0.0667 nmol/L) 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. Ultrasensitive C-Peptide Test – Cohort 2 Only

All subjects in Cohort 2 will have a blood sample drawn in conjunction with the 2-hr or 4-hr MMTT pre-stimulation (time = 0) and post-stimulation at the 90-minute (+/- 10 minutes) timepoint.

## 7.5. Implantation Procedure

Implantation occurs at Visit 3 (Day 1). The number of VC-01 units implanted will be determined in advance of Visit 3 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 availability of anatomical space for surgical implantation. All units are implanted in anatomical locations involving [redacted] suitable for implantation, as deemed appropriate by the Investigator and/or Surgeon after consultation with the Sponsor.

To conduct the procedure, [redacted]. All medications administered during the implantation procedure are to be captured in the source documents and CRF.

[redacted] Surgeons [redacted] should discuss the details of the implantation plan with the subject prior to the surgery.

[redacted]

A detailed description of the implantation procedure and surgical technique will be provided in the VC-01 Instructions for Use (IFU) and as part of site training. Site personnel are required to complete training on the procedure and handling of VC-01 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 identify the most appropriate implantation procedure to be followed [redacted] There is a possibility the implantation procedures will be modified based on data collected. To support the safety, tolerability, engraftment, and efficacy profile of VC-01, updates and additional training on the surgical procedures may occur as needed during the study.

## 7.6. Post-Implant Discharge Instructions and Assessments

Immediately following the implant procedure, the subject will remain in the clinic for up to four (4) 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 clinically-significant conditions. At the discretion of the Surgeon, the subject may be discharged earlier than four (4) hours.

Additionally, subjects will be monitored for potential immunological reactions to the implantation by traditional signs and symptoms 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 in the study database. 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 proper wound care and evaluation, and any prescribed concomitant therapies and/or treatments required to facilitate the implantation healing and engraftment process (**Section 5.3**). For the week following the implantation, subjects are advised to limit significant physical activity to ensure optimal healing (**Section 5.4**).

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.

## 7.7. 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-01.

## 7.8. 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-01.

## 7.9. Ultrasound Monitoring

Ultrasound monitoring will be performed by trained personnel either read locally at the clinical site or by a central imaging center. For consistency of results, it is recommended the same technician at the site perform all ultrasound evaluations on a subject and the same machine is used on a subject throughout the trial. Ultrasound monitoring in this study serves two purposes:

- Safety evaluations to monitor graft performance; and
- 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 at Visit 7 (Week 8), Visit 9 (Week 16), Visit 11 (Week 26), and Visit 13 (Week 52 - Cohort 2 only) or early completion/termination.

- **Location Ultrasounds**: These ultrasound evaluations will be performed within three (3) days prior to all scheduled 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 applicable Schedule of Assessments for the complete listing of when any ultrasound imaging may be required.

Clinical studies conducted by ViaCyte investigating this 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.

## 7.10. Explantation Procedure

[redacted] The VC-01 IFU outlines the 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 explanation procedure, including a reminder to contact the site if any problems occur. 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.

### 7.10.1 Explantation of Sentinel Units (Cohorts 1 and 2)

Sentinel units will be explanted at various time-points as determined by the Sponsor (refer to the Schedule of Assessments). The number of sentinels implanted will be in line with the Study Design (**Section 3** and by the Sponsor in collaboration with the Investigator and Surgeon. The decision will also be based on the available data from previous subjects and availability of anatomical space for surgical implantation. At a subject's final explant visit, all remaining sentinel units will be removed along with any dose-finding units.

### 7.10.2 Explantation of VC-01-DF Units (Cohort 2 Only)

As outlined in the Cohort 2 Schedule of Assessments, VC-01-DF units will be removed from all subjects at the end of the specific 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, explantation of up to [redacted] is allowed at any time post-implant for a subject. Explant [redacted] may occur without requiring the subject to officially withdraw from the study. Although the sentinel units implanted in subjects are expected to behave similarly to the VC-01-DF units, the explant of these VC-01-DF units is permitted and will provide additional data on the status of graft function and cell performance.

## 7.11. Histological Assessment of VC-01 Combination Product

All explanted VC-01 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 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]

In addition to endpoint analyses, the data may be used to optimize the surgical procedures and technique, the anatomical location of implants, or the perioperative care associated with VC-01. Results from these assessments will be compared to the Sponsor's database [redacted]

## 7.12. Blood Glucose Monitoring – Cohort 2 Only

Throughout the trial in both Cohorts, 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, in Cohort 2, 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 throughout Cohort 2 of this study to ensure proper glucose control:

- Laboratory tests (**Section 7.17**)
- Continuous Glucose Monitoring (**Section 7.14**)
- Self-Monitoring Blood Glucose (**Section 7.15**)

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 in Cohort 2 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 cutoff points per CGM data, SMBG blood glucose levels, exogenous insulin doses, and frequency of HEs).

In Cohort 2, 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.

## 7.13. Study Diary – Cohort 2 Only

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).

## 7.14. Continuous Glucose Monitoring (CGM) – Cohort 2 Only

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 one-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).

## 7.15. Self-monitoring Blood Glucose (SMBG) – Cohort 2 Only

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.

## 7.16. Definition, Classification, and Management of Hypoglycemic Events (HEs) – Cohort 2 Only

All SMBG or CGM values of <54 mg/dL (<3.0 mmol/L) must be captured by the subject in the diary as an HE. Additionally, if a subject does not have a blood glucose value available, but has symptoms of an 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 Cohort 2. 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.

## 7.17. Laboratory Evaluations

The protocol-required biological samples collected from subjects will be tested either at the site's local laboratory (Cohort 1) or a Sponsor-selected central laboratory (Cohort 2). Details regarding the laboratory specimen preparation, handling, storage, shipping and reporting procedures will be outlined in a separate Laboratory Manual. All protocol-required samples will be collected at the time-points indicated on the applicable Schedule of Assessments.

Other as-needed lab tests (e.g., immunosuppression drug levels, urgent medical events) will be performed by the site's local laboratories as needed.

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.

### 7.17.1. Routine Clinical Laboratory Evaluations

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

- Hematology: Hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, white blood cell (WBC) count, neutrophils (total), eosinophils, monocytes, basophils, and lymphocytes.
- Chemistry: Blood urea nitrogen (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, high density lipoprotein (HDL)-C, calculated low-density lipoprotein (LDL)-C, triglycerides, very low-density lipoprotein (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 (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 hepatitis B core and surface Ag/Ab, hepatitis C virus, and HIV (1&2).
- Other:
  - Cohort 1: HbA1C, urine pregnancy tests, Quantiferon, renal function evaluation via eGFR calculation, and thyroid stimulating hormone (screening). Drug screen at Visit 1 only.
  - Cohort 2: HbA1C, urine pregnancy tests, Quantiferon, renal function evaluation via eGFR calculation, and thyroid stimulating hormone (screening). FSH testing is required for post-menopausal women. Drug screen at Visit 1 will be analyzed at the central lab. The Visit 3 drug screen will be conducted locally using the study-provided kit.
  - Cohort 2 only: Ultrasensitive C-peptide (collected in conjunction with MMTTs pre-stimulation (time = 0) and post-stimulation at a 90-minute (+/- 10 minutes) timepoint.

### 7.17.2. Pregnancy Tests

For all women of child-bearing potential, a urine pregnancy test is administered at Visit 1, just prior to implant at Visit 3 (Day 1), and at the final explant visit (Visit 11 in Cohort 1/Visit 13 in Cohort 2) or Early Termination. Additional pregnancy tests may be completed if the Investigator suspects a possible pregnancy. Urine pregnancy testing will not be required for women who are post-menopausal (at least one complete year without menstrual bleeding in absence of any surgery

or medical condition that may cause bleeding to artificially stop) or are surgically-sterile (bi-lateral tubal ligation and tubal implants).

### 7.17.3. 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:

Blood samples will be sent to the site's local lab 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 baseline samples 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.

### 7.17.4. Inflammatory Biomarkers

Additional blood samples from subjects will be collected starting at Visit 2 and up to four (4) additional study visits for investigational assessment of inflammatory biomarkers. The number of biomarkers assessed will be limited by the amount of sample available but will not include any genetic testing. 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 study. Additional details will be provided in a study laboratory manual.

### 7.17.5. Reserve Blood Samples

Additional blood samples from subjects may be collected starting at Visit 2 and at up to five (5) additional study visits for investigational assessment of biomarkers that could be associated with the cellular viability and durability of the implanted VC-01 product. The number of biomarkers assessed will be limited by the amount of sample available but will not include any genetic testing. If the additional blood samples are collected, as much as 5 mL of blood could be collected at each time point. Results of these tests may not be reported to the site during the study. Additional details will be provided in a study laboratory manual.

### 7.17.6. Blood Volumes

#### 7.17.6.1. Cohort 1

Total blood collection volumes from scheduled visits requiring lab assessments are not planned to be greater than 200 mL over the course of Cohort 1. Of the 12 clinic visits, there are three (3) visits where blood volumes are estimated to be up to approximately 30 mL: Visit 2 (Week -1),

Visit 6 (Week 4), and Visit 11 (Week 26 or Early Termination). At other visits, the blood volume required ranges from 0 mL to 27 mL

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.

If all allowed reserve blood samples are collected, this would result in up to an additional 20 mL of blood collected for Cohort 1.

#### 7.17.6.2. Cohort 2

Total blood collection volumes from scheduled visits requiring lab assessments are not planned to be greater than 500 mL over the course of Cohort 2. Of the 14 clinic visits, there are four (4) visits where blood volumes are estimated to be up to approximately 80 mL: Visit 1 (Week -5), Visit 2 (Week -4), Visit 11 (Week 26), and Visit 13 (Week 52 or Early Termination). At other visits, the blood volume required ranges from 0 mL to 60 mL

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.

If all allowed inflammatory biomarker and reserve blood samples are collected, this would result in up to an additional ~60 mL of blood collected for Cohort 2.

# 8. SAFETY REPORTING

The Investigator is to report all directly observed AEs, all AEs spontaneously reported, or pregnancies by the study subject (or subject's partner). In addition, each study subject will be questioned about AEs and pregnancies (if applicable) at each clinic visit. As the Sponsor, ViaCyte is responsible for collecting and evaluating reported safety data in accordance with applicable regulatory requirements and as outlined in Sponsor SOPs and Safety Management Plan.

## 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] line;
- Progression/worsening of underlying disease (includes worsening diabetes)

All observed or volunteered AEs regardless of suspected causal relationship to the investigational product will be reported as described in the following sections. Non-clinically significant physical exam observations will not be reported as an AE.

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**).

Likewise, AEs may receive a temporal classification based on the start date of the event relative to when the investigational product was first administered. A treatment emergent AE (TEAE) is defined as an AE that starts on or after the date of implant surgery.

In addition, if the Investigator determines an SAE is associated with study procedures, the Investigator must record this causal relationship in the subject's 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 will 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-01, there are two (2) 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-01) itself caused or contributed to the AE.
- The surgical procedure (implantation or explanation) caused or contributed to the AE.

In evaluating the causal relationship of an AE to VC-01 and the surgical procedures, 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 the subject's source records.

Relationship of an AE to VC-01 and the surgical procedures will be assessed as follows:

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

**Unlikely Related:** A clinical event including laboratory test abnormalities without any temporal relationship to the investigational product exposure or the surgical procedures which makes a causal relationship doubtful or unlikely and/or in which other drugs, chemicals, or underlying disease provides plausible explanations.

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

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

### 8.1.2. Expected Adverse Reactions

Refer to **Section 1.4.2.1**.

### 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 any 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-01. 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 sentinel or dose-finding (VC-01-DF) units are considered AESI.
- AEs that result in early withdrawal from the study.
- Severe hypoglycemic events occurring after VC-01 implantation possibly or definitely related to VC-01.

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 for Cohort 1 with a start date occurring between Visit 3 (Day 1) and through the last subject visit must be recorded on the CRF. All AEs for Cohort 2 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, and 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 and pregnancies 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 separate follow-up study. Further details on how to report ongoing AEs spanning the period between this protocol and the separate follow-up study will be outlined in the separate follow-up protocol.

All AE reporting, including SAEs and suspected unexpected serious adverse reactions (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-01 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 using the Sponsor's SAE Reporting Form 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 using the Sponsor's Pregnancy Report Forms.

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. Hypoglycemic Events

In Cohort 1, all hypoglycemic events occurring during study participation are expected to be unrelated to the investigational product. The number of sentinel units implanted in subjects enrolled into this study results in a sub-therapeutic dose. Additionally, multiple sentinels will be explanted prior to the units reaching the potential for functional engraftment. Therefore, the amount of endogenous insulin released from implanted VC-01 units is expected to have no effect on glycemic control.

Therefore, since hypoglycemia is a symptom of the disease under study, routine hypoglycemic events will not be captured as adverse events in Cohort 1.

However, throughout Cohort 2, hypoglycemic events and severe hypoglycemic events (SHE) will be captured as described in **Section 7.16**.

## 8.4. Reporting of Pregnancy

For investigational products, an exposure during pregnancy (also referred to as Exposure in Utero [EIU]) occurs if an enrolled female subject becomes, or is found to be, pregnant while in the study.

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 subject's partner) becomes or is found to be pregnant during the study, the Investigator must submit this information to the Sponsor on a Pregnancy Report Form. This must be done within 24 hours of awareness of the event. The information submitted should include the anticipated date of delivery (if known). See below for information related to termination of pregnancy. All confirmed EIU cases and follow-up information will be recorded in a Pregnancy Safety Database.

Follow-up is conducted to obtain pregnancy outcome information for all pregnancy 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 Pregnancy Report 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).

## 8.5. Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) is available to meet throughout the study to review accumulated data at the request of the Sponsor. There are no required DSMB meetings specific to the administration of this trial during Cohort 1. Any DSMB meetings conducted during Cohort 1 will be performed on an ad hoc basis. During Cohort 2, it is anticipated that the DSMB will meet on a regular basis to review accumulating data from the study.

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:

- Cohort 1: Any DSMB meetings conducted during Cohort 1 will be on an ad hoc basis. After a minimum of three (3) subjects from Cohort 1 have reached the Week 4 clinic visit and the data are available, the Sponsor may request that the DSMB meet to review the accumulated data.
- Cohort 2: Once Cohort 2 begins enrollment, the DSMB will meet 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 by the Sponsor or the DSMB.

## 8.6. Study Stopping Rules

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

1. Two or more subjects have pronounced immune responses to VC-01.
2. Two or more subjects experiencing an 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-01. 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-01 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-01. The DSMB can also recommend treatment continue for a shorter duration (i.e., less than the planned 6 months (Cohort 1) or 12 months (Cohort 2)) 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-01 units explanted, and all subjects will be monitored post-explant in the separate follow-up safety study.

# 9. CLINICAL MONITORING

Routine on-site and/or remote monitoring visits 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 (including what data may be verified in person versus remotely), 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 Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. If the DSMB is requested to review the data from Cohort 1, the study SAP will be written and approved prior to the Cohort 1 data cut-off (e.g., the data through Week 4 for the final subject in Cohort 1 whose data is part of the DSMB data review).

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 sentinel units in Cohort 1 or initially implanted VC-01-DF dose-finding units in Cohort 2. In Cohort 1, if a subject has a sentinel 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 sentinel units originally implanted. For Cohort 2, if a subject has a VC-01-DF unit explanted for any reason and remains in the study, then she/he will be included in the treatment group that is described by the number of VC-01-DF units originally implanted. If a Cohort 2 subject has no VC-01-DF units implanted, but has sentinel units implanted, then the subject will be included in the “0 implanted VC-01-DF units” treatment group for Cohort 2. If, during the course of the study, further enumeration is needed to differentiate treatment group (for example, if it is necessary to differentiate multiple EDDS configurations used in Cohort 1), then that further detail will be included in the study SAP.

Where appropriate, data from subjects in Cohort 1 and in Cohort 2 will be summarized together (within the same table). When data from the two cohorts is included in the same table, the treatment group will be used to differentiate the data from Cohort 1 and Cohort 2.

## 10.1. Study Hypotheses

There are no statistical hypotheses being tested.

## 10.2. Sample Size Considerations

In Cohort 1, up to 30 subjects will be enrolled. In Cohort 2, up to 40 subjects will be enrolled, for a total enrollment of up to 70 subjects in both cohorts.

The 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 30 subjects should allow for adequate assessment of Cohort 1 study objectives.

A sample size of 40 subjects in Cohort 2 [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 will provide [redacted].

For the 2-hour MMTT, a sample size of 40 subjects [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. A descriptive analysis may be produced when all subjects in Cohort 2 have reached 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 early phase 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.

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

Additional safety event adjudication committees may be established as appropriate. As described above, individual committee charters will provide specific descriptions of the scope of

responsibilities and the processes and definitions used to review and assess specific safety events and enrollment.

## 10.4. Analysis Plan

### 10.4.1. Analysis Populations

The Full Analysis Set (FAS) is defined as all subjects who were enrolled into the study and received implantation of at least one sentinel unit and/or VC-01-DF dose-finding unit on Study Day 1/Visit 3. The FAS will be used for all efficacy summaries/analyses and listings.

The Safety Analysis Set (SAS) is defined as all subjects who were enrolled into the study and in whom an implant surgery was attempted, regardless if any sentinel or dose-finding units were actually implanted. The SAS will be used for safety summaries and listings.

### 10.4.2. Demographic and Subject Characteristics

Demographic information and subject characteristics such as gender, race, age, and baseline vital signs will be summarized by treatment group for Cohort 1 and Cohort 2. Pertinent medical history will also be summarized similarly.

### 10.4.3. Primary Analysis

#### 10.4.3.1. Cohort 1 Primary Analysis

The FAS will be used for the histology summarizations for Cohort 1 subjects, which include the [redacted]; the [redacted]

The [redacted], summarized by time point and treatment group. The Sponsor initially plans to explant the majority of sentinel units at the Visit 6/Week 4 and Visit 8/Week 12 time points. However, as data is collected in the trial, it may inform that evaluation at additional time points is required.

[redacted] treatment group for Cohort 1. Additional details will be outlined in the SAP.

#### 10.4.3.2. Cohort 2 Primary Analysis

For Cohort 2 subjects, the FAS will be used to analyze the primary efficacy endpoint, the change from baseline to Week 26 in C-peptide $AUC_{0\text{-}4h}$ following an MMTT.

The endpoint 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 output from the ANCOVA will include the least squares mean (LSM) and standard error (SE) for each treatment group.

### 10.4.4. Secondary Analysis

#### 10.4.4.1. Cohort 1 Secondary Analysis

For the Cohort 1 subjects, the FAS will be used to perform the qualitative assessment of the severity of the host immune response as rated at post-implant time points. These results will be summarized by explant time point, anatomical location, and treatment group.

The number of Cohort 1 subjects experiencing off-target growth as evidenced by implanted VC-01 units via lumen ultrasound measurements or by histological examination of explants will be summarized by treatment group.

Unless otherwise specified, the SAS will be used for the safety summarizations for the Cohort 1 subjects. 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 for the Cohort 1 subjects. Where appropriate, change from baseline in safety data will also be summarized in a similar manner.

The number of Cohort 1 subjects undergoing a premature VC-01 unit explant will be provided in a listing which includes the reason for explantation (i.e., safety issue, malfunction, damaged, planned explant, etc.).

For the secondary safety endpoint of immune response as measured by serum immunoglobulin and hematological assays, any Cohort 1 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 in Cohort 1. 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 Cohort 1 subjects with the symptom at that time-point will be summarized by treatment group and overall.

#### 10.4.4.2. Cohort 2 Secondary Analyses

##### 10.4.4.2.1. Cohort 2 Secondary Safety Analyses

Unless otherwise specified, the SAS will be used for the safety summarizations for the Cohort 2 subjects. 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. As with the Cohort 1 subjects, the summarization of AEs for Cohort 2 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, clinical laboratory data, and hypoglycemic events will be summarized by study visit and treatment group, for the Cohort 2 subjects. Where appropriate, change from baseline in safety data will also be summarized in a similar manner. Changes in physical examinations will be summarized by treatment group and overall, for the Cohort 2 subjects. Non-diabetic concomitant medications will also be summarized by treatment group and overall.

The number of Cohort 2 subjects experiencing off-target growth as evidenced by implanted VC-01 units via lumen ultrasound measurements, or by histological examination of explants will be summarized by treatment group.

For immune response as measured by serum immunoglobulin and hematological assays, any Cohort 2 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.

Implantation site assessments will be summarized at each time-point post-implantation and each visit thereafter. For each site assessment symptom, the number of Cohort 2 subjects with the symptom at that time-point will be summarized by treatment group and overall.

Finally, the number of Cohort 2 subjects undergoing a premature VC-01 unit explant will be provided in a listing, which includes the reason for explantation (i.e., safety issue, malfunction, damaged, planned explant, etc.)

#### 10.4.4.2.2. Cohort 2 Secondary Efficacy 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.

The FAS will be used to analyze the secondary efficacy endpoints, with the analysis for each endpoint performed within Cohort 2 subjects only. Change from baseline to Weeks 16, 20, 26 and 39 in C-peptide $AUC_{0\text{-}2h}$ following an MMTT and change from baseline to Week 52 in C-peptide $AUC_{0\text{-}4h}$ following an MMTT; change from baseline to Weeks 16, 20, 26, 39 and 52 in average daily insulin dose in the seven days preceding the clinic visit; and change from baseline to Weeks 16, 20, 26, 39 and 52 in time in euglycemic range, time in hypoglycemic range, and time in hyperglycemic range will each 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 an MMTT will be assessed using Kaplan-Meier curves, with the p-value from the logrank test also provided.

The percent of subjects who achieve a positive stimulated C-peptide (defined as > 0.2 ng/mL) after implant; the percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose from baseline to Weeks 16, 20, 26, 39 and 52; and the percent of subjects who achieve exogenous insulin independence, percent of subjects (of those achieving insulin independence) achieving HbA1c $\leq$ 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).

Finally, the percent of time spent with blood glucose values at various cut points as measured by each subject's CGM 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, >180 mg/dL and ≥ 250 mg/dL) and for each treatment group.

#### 10.4.4.2.3. Cohort 2 Secondary Exploratory Analyses

In Cohort 2, the FAS will be used for the [redacted].

The [redacted], summarized by treatment group and time point. The Sponsor may explant sentinel units beginning at the Week 4 time point. However, as data is collected in the trial, it will inform that evaluation at additional time points may be required.

The percentage of [redacted] summarized by treatment group and time point. The Sponsor will [redacted]

Histology results will be summarized by explant time point, anatomical location, and treatment group for Cohort 2. Additional details will be outlined in the SAP.

## 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 (whether on site or via remote access as described in associated monitoring plan). 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 (GCP) 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 are 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 (whether on paper or through electronic data capture system) must be comply 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 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.

## 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.

## 13.6. Reasons for Withdrawal

Investigators will make reasonable efforts to keep enrolled subjects in the study. However, if a subject is prematurely removed from treatment, a termination visit must be performed. This would generally include all procedures outlined in Visit 11 (Week 26) for Cohort 1 and Visit 13 (Week 52) for Cohort 2 as well as the procedures outlined in follow-up Visit 12 (Week 27) for Cohort 1 and Visit 14 (Week 53) for Cohort 2. 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.

**Cohorts 1 and 2**

- Subject has a new onset, off-target cell growth within the unit confirmed by a board-certified pathologist as a teratoma and is considered related to VC-01.
- Subject appears to mount an immune 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 (**Section 5.4.4)**.
- 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 unit may occur in this situation without requiring the withdrawal of the subject from the study upon request from the Sponsor.

**Cohort 2 Only**

- After a minimum of eight weeks post-implantation, the subject experiences three or more Severe Hypoglycemic Events (SHE) over a six-month period unrelated to anything other than VC-01. This assumes the SHE occurred despite reasonable adjustments in the exogenous insulin requirements and appropriate dietary adjustments.

If a subject meets any of these criteria, any remaining 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.

**Note:** *A subject whose final explant is expedited at the request of the Sponsor to occur prior to Week 26 (Cohort 1) or Week 52 (Cohort 2) for reasons unrelated to safety issues (e.g., the Sponsor would like to collect all explant data from the subject by Week 12) will be categorized as having completed the study. These subjects will not be classified as Early Terminations.*

### 13.6.1. Handling of Withdrawals

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. It is recommended that 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 source 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 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 separate, 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 8.2**. 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 11/ET and Visit 12 (Cohort 1) or Visit 13/ET and Visit 14 (Cohort 2) 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 11/ET and Visit 12 (Cohort 1) or Visit 13/ET and Visit 14 (Cohort 2) procedures. These procedures should be completed as described for early withdrawal subjects in **Section 13.6**.

## 13.8. Future Evaluation of Explanted Units

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

# 14. DATA HANDLING AND RECORD KEEPING

## 14.1. Data Management Responsibilities

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

## 14.2. Data Capture Methods

The Investigator shall capture data in the form and manner required by the Sponsor. The Investigator has ultimate responsibility for the collection and reporting of all clinical and safety data entered on the CRFs and any other data collection forms (e.g., source documents) and ensuring that they are accurate, authentic, original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The Investigator or appropriate site personnel must sign (electronically or hard copy) the CRF(s) to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be completed using Good Documentation Practices. .

## 14.3. Types of Data

In most cases, the source documents (the first recording of the data) include, but are not limited to, the hospital's or the physician's subject chart, laboratory reports, etc. The data collected on the CRFs must match the source data. 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 as applicable for each cohort (e.g., safety labs, MMTT, CGM blood glucose data, chemistry, 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 Trial Agreement (CTA), 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 or generated systematically 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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