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 Statistical Analysis Plan

Final Version 1.0

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ViaCyte Inc.

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Statistical Analysis Plan (SAP)

PROTOCOL 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

SAP Version 1.0

Version	Date	Comment
1.0	15Mar2021	Original version

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1 Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDDS	Encaptra Drug Delivery System
eGFR	Estimated Glomerular Filtration Rate
ET	Early Termination
FAS	Full Analysis Set
FSH	Follicular Stimulating Hormone
HbA1C	Hemoglobin A1C
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HE	Hypoglycemic Event
hESC	Human Embryonic Stem Cells
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICD	Informed Consent Discussion
LSM	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed Meal Tolerance Test
PEC-01	Pancreatic Endoderm Cells
PRA	Panel Reactive Antibody
PT	Preferred Term
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
T1DM	Type 1 Diabetes Mellitus
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
VC-01	VC-01™ Combination Product
VC-01-DF	VC-01 Dose-Finding Unit

2 Introduction

The purpose of this statistical analysis plan (SAP) is to describe in detail the procedures and statistical methods required for completing the final analysis of data in accordance with Protocol 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 (T1DM)*.

Any text in this SAP that comes directly from the Protocol is shown in *italic* font.

3 Study Overview

3.1 Study Population

Subjects with T1DM will be enrolled into this clinical trial.

3.2 Study Design

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

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 will be used in this study; hence the term "EDDS configuration" represents a unique version of the EDDS.

Subjects may be implanted with VC-01-DF combination product (for dose-finding) and smaller sentinel combination product. VC-01-ST and VC-01-20 are different configurations of sentinels. The term "sentinel" encompasses both of these smaller units unless specified. These are smaller units that will be explanted at various time points and examined histologically ex vivo.

<u>Cohort 1– Safety and Engraftment</u>
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
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.

3.3 Study Assessments

Visits will include assessments such as physical examinations (complete, abbreviated, or targeted), 12-lead ECGs, vital signs (sitting blood pressure, pulse rate and temperature) and body weight, ultrasound monitoring, laboratory evaluations, and adverse event collection. *Histological assessment of the units will be performed by ViaCyte or a designee,* after explantation. *Histological assessment of the units may include but is not limited to:*

- *Survival of implanted cells via cell nuclei count through hematoxylin and eosin staining.*
- *Differentiation of PEC-01 to endocrine cells (e.g., α-cells, β-cells, and/or δ-cells) via immunohistochemical staining.*
- *The host tissue inflammatory or immunological response in the tissue capsule.*

Blood glucose monitoring is performed through various methods throughout Cohort 2 of this study to ensure proper glucose control. Investigators will review the blood glucose data at each study visit.

3.4 Anticipated Number of Subjects

Total enrollment will be up to 70 subjects. 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.

4 Study Objectives and Endpoints

4.1 Objectives:

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 from implantation to Month 6/Week 26 or earlier if requested by the Sponsor.*

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.*

4.2 Endpoints:

The study endpoints for each Cohort are as follows:

Cohort 1 Study Endpoints
Primary Endpoints:

- *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 Endpoints:

- *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* (lumen thickness > 1 mm)*, or by histological examination of explants.*
- *The* confirmed *incidence of immune sensitization defined by presence of donor anti-HLA (human leukocyte antigen) antibodies absent prior to implant* in conjunction with either confirmatory histological observations from at least one explanted unit and/or the presence of clinical symptoms. Once sensitization has been confirmed by ViaCyte, an AE of 'sensitization' will be entered into the clinical study database.

Cohort 2 Study Endpoints
Primary Endpoint:

- *Change from baseline to Week 26 in C-peptide $AUC_{0\text{-}4h}$ following a mixed meal tolerance test (MMTT).*

Secondary Endpoints:
Safety and Tolerability

- *Comprehensive profile of VC-01 combination product implanted for up to Month 12/Week 52 as measured by:*
  - *All reported AEs.*
  - The incidence of off-target growth as evidenced by implanted VC-01 units via lumen ultrasound (lumen thickness > 1 mm) measurements, or by histological examination of explants.
  - *The* confirmed *incidence of immune sensitization defined by presence of donor anti-HLA antibodies absent prior to implant* in conjunction with either confirmatory histological observations from at least one explanted unit and/or the presence of clinical symptoms.
  - *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, and 39 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.*
- *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.*
- Change from baseline to Weeks 16, 20, 26, 39, and 52 in weekly frequency of hypoglycemic events;
- Change from baseline in frequency of hypoglycemic events (24-hour; daytime [start between 6a.m.-12a.m.]; nocturnal [start between 12a.m.-6a.m.]) to Weeks 16, 20, 26, 39 and 52.
- Percent of subjects free of severe hypoglycemic events between study visits starting with Week 16 (i.e., Weeks 16-20, Weeks 20-26, Weeks 26-39, Weeks 39-52/ET, and Weeks 16-52/ET).

Exploratory Endpoint:

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

5 Analysis Plan Overview

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 those subjects.

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 Data Safety Monitoring Board (*DSMB*) *available.*

The final summarization of the data will be performed after official database lock, once the last subject in Cohort 2 has completed his/her Week 53/Follow-up visit.

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 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 no VC-01-DF units are implanted into a Cohort 2 subject*, but sentinel units are implanted, then the subject will be included in the "0 implanted VC-01-DF units" treatment group. 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 this *study SAP* (that is, this SAP will be amended to include that information).

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.

All data that are collected in the study will be provided in a listing. In general, listings will be sorted by Cohort, then treatment group, investigative site and subject number, and, where appropriate, study visit/start date.

6 Analysis Sets

6.1 Full Analysis Set

The Full Analysis Set (FAS) is defined as all subjects who were enrolled into the study and received implantation of at least one sentinel 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.

6.2 Safety Analysis Set

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.

7 Statistical Analyses

7.1 Statistical Power and Sample Size Considerations

There are no statistical hypotheses being tested.

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 other 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 will [redacted]

7.2 Baseline, Endpoint and Missing Value Definitions

7.2.1 Baseline

Baseline will be defined as the last non-missing value prior to the start time of the surgical implantation procedure unless otherwise specified. For MMTTs in Cohort 2 subjects, the 4-hour MMTT performed during the Screening period is used for defining both the baseline 4-hour MMTT and the baseline 2-hour (using the first 2 hours of data) MMTT.

7.2.2 Analysis Visit Windows

For the purpose of analyzing time to event endpoints, the time-in-study for each subject will be measured relative to Day 1, the day that the surgical implantation procedure was attempted.

The data will be summarized based on the electronic case report form (eCRF) (Study Visit) in which it was collected as long as the data are within the windows specified. If data for a particular Study Visit is not within the windows specified, then queries will be sent to the site to confirm data entry. Data collected as an unscheduled visit will be re-assigned to a Study Visit based on the SAP visit windows specified.

Because subjects are not always able to complete visits on the scheduled target day, visit windows will be used for associating data with specific time points. The visit windows are given below.

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.

Cohort 1 Visit Windows

Visit Label	Target Day	Window for Summarization
V1 Screen (Week -2)	-14	≤ -11
V2 Screen (Week -1)	-7	[-10, -1]
V3 Enroll (Day 1)	1	[1]
V4 (Day 2)	2	[2, 8]
V5 (Week 2)	15	[9, 22]
V6 (Week 4)	29	[23, 43]
V7 (Week 8)	57	[44, 71]
V8 (Week 12)	85	[72, 99]
V9 (Week 16)	113	[100, 127]
V10 (Week 20)	141	[128, 162]
V11 (Week 26)	183	[163, 186]
V12 (Week 27/Follow-up)	190	≥187

Cohort 2:

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.

Cohort 2 Visit Windows

Visit Label	Target Day	Window for Summarization
V1 Screen (Week -5)	-35	≤ -32
V2 Screen (Week -4)	-28	[-31, -1]
V3 Enroll (Day 1)	1	[1]
V4 (Day 2)	2	[2, 8]
V5 (Week 2)	15	[9, 22]
V6 (Week 4)	29	[23, 43]
V7 (Week 8)	57	[44, 71]
V8 (Week 12)	85	[72, 99]
V9 (Week 16)	113	[100, 127]
V10 (Week 20)	141	[128, 162]
V11 (Week 26)	183	[163, 228]
V12 (Week 39)	274	[229, 319]

V13 (Week 52)	365	[320, 368]
V14 (Week 53/Follow-up)	372	≥ 369

7.2.3 Replicate Data

For data summarization and/or analysis for each parameter, if multiple study visits (including unplanned visits) occur within the same visit window, then precedence will be given to the study visit at which an MMTT was performed. If no MMTT was performed at either visit, then if there is a study visit and an unplanned visit within the same window, then the data from the study visit will be used. Otherwise, the study visit on the day that is closest to the target day will be used, as long as there are data for that parameter. All data from all study visits (planned, unplanned, and replicate)will be provided in the data listings.

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7.2.4 Missing Data

MMTTs are performed in Cohort 2 subjects and will require a minimum of two timepoints in order to be considered evaluable. Any missing timepoints will be imputed using the following rules:

For C-peptide and blood glucose values:

- If the final timepoint is missing, it will be imputed as the average of the last available timepoint and zero (the value '0'). If consecutive, final timepoints are missing, this function will be performed twice (once for each timepoint).
- If a middle timepoint is missing, it will be imputed as the average the two neighboring timepoints. If consecutive, middle timepoints are missing, both values will be imputed as the average of the two closest, neighboring values on each side.

C-peptide value only:

- If the 0 minute timepoint is missing, the value will be imputed as zero (the value '0'). If multiple timepoints were missed at the start of an MMTT, the timepoints will be imputed in reverse order (starting with the latest missing timepoint). The missing timepoint(s) will be imputed as one-half the value of the subsequent timepoint.

Blood glucose value only:

- If a first timepoint is missing, the value will be imputed as the average of the first available timepoint and zero (the value '0'). If multiple timepoints were missed at the start of an MMTT, the timepoints will be imputed using this same formula, in reverse order (starting with the latest missing timepoint and repeating for each subsequent missing value until the 0 minute timepoint has been imputed).

For AEs, it is expected that complete start and end dates will be provided for all reported AEs. Therefore, no imputation for missing or partial dates is needed for AEs. No additional imputations will be performed for any other missing data in this study.

7.2.5 Change From Baseline

Change from baseline is defined as:
Value of parameter post-baseline – Value of parameter at baseline

If the post-baseline value for a specific parameter at a specific timepoint is missing, then the change from baseline at that timepoint will not be calculated. The subject will not be included in the change from baseline at that timepoint, for that parameter (but will be included in the change from baseline for other timepoints where the subject has post-baseline data for that same parameter).

7.2.6 Data Derivations and Transformations

7.2.6.1 C-peptide $AUC_{0\text{-}4h}$ and $AUC_{0\text{-}2h}$

Cohort 2 subjects will undergo MMTTs. The area under the curve (AUC) for each MMTT is calculated by adding the areas under the curve between each pair of consecutive observations. The calculation is based on the trapezoidal rule:

$$AUC = \frac{1}{2}\sum_{i=1}^{n-1}(t_{i+1} - t_i)(y_i + y_{i+1})$$

Where there are n C-peptide measurements y_i at nominal time points t_i (i=0,….,n-1), and $(t_i+1 - t_i)$ will be measured in hours.

Specifically,

$$AUC_{0\text{-}4h} = 0.5(y_0 + y_{0.5})/2 + 0.5(y_{0.5} + y_1)/2 + 0.5(y_1 + y_{1.5})/2 + 0.5(y_{1.5} + y_2)/2 + 1(y_2 + y_3)/2 + 1(y_3 + y_4)/2$$

$$AUC_{0\text{-}2h} = 0.5(y_0 + y_{0.5})/2 + 0.5(y_{0.5} + y_1)/2 + 0.5(y_1 + y_{1.5})/2 + 0.5(y_{1.5} + y_2)/2$$

Two-hour MMTTs will be conducted at Visit 7/Week 8; Visit 8/Week 12; Visit 9/Week 16; Visit 10/Week 20; and Visit 12/Week 39; 4-hour MMTTs will be conducted at Screening; Visit 11/Week 26; and Visit 13/Week 52 or Early Termination. C-peptide results reported as ≤0.1 ng/mL will be imputed as 0 for determination of the $AUC_{0\text{-}4h}$ and $AUC_{0\text{-}2h}$.

An unscheduled MMTT time point measurement will be mapped to be a scheduled time point measurement for AUC calculation if: 1) A scheduled time point measurement is missing; and 2) The time of the unscheduled sample collection is within a 10-minute sampling window for that scheduled time point except for the last scheduled time point. Specifically, within 10 minutes after the start time of Boost Hi-Protein drink for the 0 minute time point; between 20 and 40 minutes after the 0 minute time point sampling, for the 30 minute time point; between 50 and 70 minutes after the 0 minute time point sampling, for the 60 minute time point; between 80 and 100 minutes after the 0 minute time point sampling, for the 90 minute time point; between 110 and 130 minutes after the

0 minute time point sampling, for the 120 minute time point; and between 170 and 190 minutes after the 0 minute time point sampling, for the 180 minute time point. If the last scheduled time point (120 minute time point for a 2-hour MMTT or 240 minute time point for a 4-hour MMTT) is missing and if there is an unscheduled time point that is after the last scheduled time point, the unscheduled measurement will be mapped to be the last time point measurement. For example, if the 240 minute time point is missing for a 4-hour MMTT, but there is a measurement at 270 minutes, then the measurement from the 270 minute time point will be used, with a time point value of 240 minutes.

After the mapping of unscheduled time point measurement(s), if any C-peptide measurement is still missing, the imputation rules specified in Section 7.2.4 will be applied.

7.2.6.2 Time to Onset of Biological Response of C-peptide Following MMTT

The biological response of C-peptide is defined as a value >0.2 ng/mL for the C-peptide measurement. For Cohort 2 subjects, time to onset of biological response of C-peptide will be calculated in two ways: the time to onset of biological response from implantation, and the time to biological response within each MMTT.

For the time to onset of biological response from implantation, the time unit will be 'days' and the time itself will be calculated as:

> Time to onset of biological response of C-peptide (days) =
> (Date of first MMTT at which the subject achieved at least one C-peptide > 0.2 ng/mL) – (Date of surgical implantation procedure for the subject) + 1

For the time to onset of biological response within each MMTT, the time unit will be 'minutes' and the time itself will be calculated as:

> Time to onset of biological response of C-peptide (minutes) =
> (Time during MMTT at which the subject first achieved a C-peptide > 0.2 ng/mL) – (Start time of Boost Hi-Protein drink for the MMTT for the subject)

For these time-to-event analyses, subjects who did not achieve biological response will be censored. That is, for the time to onset of biological response of C peptide from implantation, subjects who did not achieve at least one C-peptide > 0.2 ng/mL during any MMTT will be censored at the time they leave the study (complete the study, or withdrawal from the study).

For the time to onset of biological response within each MMTT, subjects who did not achieve at least one C-peptide within a 4-hour MMTT will be censored at 240 minutes. Subjects who did not achieve biological response of C-peptide during a 2-hour MMTT will be censored at 120 minutes.

7.2.6.3 Average Daily and Weekly Exogenous Daily Insulin Dose and Exogenous Insulin Independence

Exogenous daily insulin dose logs will be completed via subject diary by subjects in Cohort 2. Investigators will review the exogenous insulin dose logs completed by the subjects at each study visit. Determination of exogenous insulin dosage levels and exogenous insulin independence for Cohort 2 subjects will be determined based on the subjects' insulin dose logs.

Blank values in the insulin log are not considered to be 0 values.

7.2.6.3.1 Daily and Weekly Exogenous Insulin Dose

For subjects in Cohort 2, baseline average daily and average weekly exogenous insulin dose requirements will be calculated using up to 28 days of data. Baseline average daily and average weekly insulin requirements will be calculated using data starting at Day -1 (the day prior to implant) and working backwards for up to 28 days (through Day -28). For instances in which the available pre-implant data provides less than 28 days of data, post-implant data will be used to supplement, using Day 4 forward until 28 days of data are available. Data from days on which an MMTT or SOGCT was performed, will not be included in the calculation.

At Weeks 16, 20, 26, 39 and 52, the last 7 daily total exogenous insulin doses recorded in the log will be used to calculate the average daily and weekly exogenous insulin dose at that visit. The last 7 daily records must be within the previous 14 calendar days and may not include a day in which an MMTT or SOGCT was performed. There must be at least 4 different days worth of data for a particular timepoint to be considered evaluable.

The weekly average value will be calculated as:

> 7 * (sum of the insulin doses during the period / number of days with insulin doses in the period).

The percent reduction in average weekly exogenous insulin dose from baseline at these visits will be calculated as:

> (Average weekly insulin dose at post-baseline visit - baseline average weekly insulin dose)*100/ baseline average weekly insulin dose.

7.2.6.3.2 Exogenous Insulin Independence

For subjects in Cohort 2, exogenous insulin independence will be defined in two ways.

First, achieving exogenous insulin independence will be defined as having an exogenous insulin dose of 0 for a minimum of any 14 consecutive days during the study, based on the data from exogenous daily insulin dose logs. Days that are missing or blank on the insulin log are not considered to be 0 values.

The second definition of exogenous insulin independence includes having an exogenous insulin dose of 0 for a minimum of any 14 consecutive days (the first definition of insulin independence) in addition to having HbA1c ≤ 7.0%, and (2-hour or 4-hour) MMTT fasting (at the start of the MMTT) glucose ≤ 125 mg/dL and 120-minute glucose ≤ 180 mg/dL. The HbA1c value and the MMTT glucose values will be those values obtained at a clinic visit that is closest temporally to the 14 consecutive days of 0 exogenous insulin dose. Depending on when the 0 doses of insulin begin, it is possible that the closest value temporally for HbA1c may be from a different clinic visit than the closest value temporally for glucose from the MMTT.

7.2.6.4 Percent of Time Spent with Blood Glucose Values at Various Cut Points

Cohort 2 subjects will be provided with a CGM system by the Sponsor and are required to use the Sponsor-provided CGM during study participation. The blood glucose value cut points of <54 mg/dL, ≥54 to <70 mg/dL, ≥70 mg/dL to ≤180 mg/dL, >180 mg/dL and >250 mg/dL will be assessed.

The assessment of blood glucose cut points will be performed three ways: over the entire 24-hour time period, over the nocturnal (CGM value below/above the cut point occurs between 12 a.m. – 6 a.m.) time period, and over the daytime (CGM value below/above the cut point occurs between 6 a.m. – 12 a.m.) time period.

Baseline CGM data will be utilized to calculate percentages of time spent with blood glucose values at the various cut points for up to 28 days, starting at Day -1 (i.e., the day prior to implant) and working backwards for up to 28 days (through Day -28). For instances in which the available pre-implant data provides less than 28 days of data, post-implant data will be used, from Day 4 forward until 28 days of data are available. In addition, the CGM data from the 14 days prior to each scheduled clinic visit will be used to calculate percentages spent with blood glucose values at the various cut points for these visits. For all timepoints (baseline and on-study), data should not be used if an SOGCT (baseline only) or MMTT was performed on that day.

7.2.6.5 Frequency of HEs using Subject-Reported Diary Data

HE data collected from the subject-completed diaries will be used for assessment of efficacy. Investigators will review the HE logs in the diary at each study visit. Blank values in the HE log are considered to be 0 values.

HEs will be classified in six ways: total HEs, severe HEs (SHEs), nocturnal HEs, severe nocturnal HEs, daytime HEs, and severe daytime HEs. Total HEs are HEs that occur at any time during the 24-hour period; SHEs are HEs requiring the aid of another person to administer carbohydrates, glucagon, or other resuscitative assistance any time during the 24-hour period. Nocturnal HEs are HEs that start during the 12 a.m. – 6 a.m. period; severe nocturnal HEs are SHEs that start during the 12 a.m. – 6 a.m. period. Daytime HEs are HEs that start during the 6 a.m. – 12 a.m. period; severe daytime HEs are SHEs that start during the 6 a.m. – 12 a.m. period.

The baseline average weekly frequency of subject-reported HEs, SHEs, nocturnal HEs, severe nocturnal HEs, daytime HEs and severe daytime HEs will be calculated using up to 28 days of data. The baseline average weekly frequency will be calculated using data starting at Day -1 (i.e., the day prior to implantation) and working backwards for up to 28 days (through Day -28). For instances in which the available pre-implant data provides less than 28 days of data, post-implant data will be used from Day 4 forward until 28 days of data are available. Data from days on which the Screening SOGCT or the MMTT was performed will not be used in the calculation.

The total number of HEs, SHEs, nocturnal HEs, severe nocturnal HEs, daytime HEs, and severe daytime HEs occurring in the 14 days prior to each specified time point (Weeks 16, 20, 26, 39, and 52) will be used to calculate the weekly frequency of total HEs, SHEs, nocturnal HEs, severe nocturnal HEs, daytime HEs, and severe daytime HEs, respectively, at the specified time point. Data for HEs/SHEs should not be used if an MMTT was performed on that day.

7.2.6.6 Frequency of HEs using CGM Data

CGM will be utilized, based on the below specified rules, to evaluate the number of hypoglycemic episodes (number of times blood glucose falls below 70 mg/dL) and the number of severe hypoglycemic events (number of times blood glucose falls below 54 mg/dL) for each subject:

- A set of CGM readings < 70 mg/dL or <54 mg/dL, with a minimum overall duration of 15 minutes
- Up to two consecutive readings >= 70 mg/dL (or >= 54 mg/dL for separate summary) are allowed within the same episode
- If a subsequent episode starts within 60 minutes of the start of the previous episode, then they are combined and counted only as one episode

The total number (over the entire 24-hour time period) of episodes will be calculated as well as the number of nocturnal (starts during the 12 a.m. – 6 a.m. period) episodes and the number of daytime (starts during the 6 a.m. to 12 a.m.) episodes.

Baseline CGM-reported HE data will be calculated using up to 28 days of data. Baseline CGM-reported HEs will be recorded starting at Day -1 (i.e., the day prior to implant) and working backwards for up to 28 days (through Day -28). For instances in which the available pre-implant data provides less than 28 days of data, post-implant data will be used from Day 4 forward until 28 days of data are available. These data will be used to calculate the baseline number of weekly total episodes, weekly nocturnal episodes, and weekly daytime episodes. In addition, the CGM data from the 14 days prior to each scheduled clinic visit will be used to calculate the number of weekly total episodes, the number of weekly nocturnal episodes, and the number of weekly daytime episodes for each of these visits. For baseline and on-study time points, data from days on which an SOGCT (baseline only) or MMTT was performed should not be used.

7.2.6.7 Early Termination (ET) Visit Mapping

For safety data from ET visits, the data will not be mapped. For subjects in Cohort 1, ET visits will be combined with Week 26 visits, and the time point labelled "Week 26/ET." For subjects in Cohort 2, ET visits will be combined with Week 52 visits, and the time point labelled "Week 52/ET."

For efficacy data from ET visits, the data will be mapped using the analysis visit window and the data handling rules as defined in Section 7.2.2 and 7.2.3. These mapped analysis visit data will be used for analyses and summaries.

7.3 Statistical Analyses

7.3.1 Disposition

Subject disposition will be summarized by treatment group and overall, as appropriate. The disposition summary will include:

- Number of subjects screened;
- Number and percent of subjects who failed screening and screen failure reasons;
- Number of subjects included in the SAS;
- Number of subjects included in the FAS;
- Number and percent of subjects in Cohort 1 and in Cohort 2 who completed as per protocol for both the FAS and the SAS;
- Number and percent of subjects in Cohort 1 and Cohort 2 who withdrew prior to completing the study, and associated primary reason for withdrawal, for both the FAS and the SAS.

7.3.2 Protocol Deviations

All protocol deviations will be listed, sorted by Cohort, then treatment group, investigative site and subject number, and date of protocol deviation.

7.3.3 Study Drug Administration

The length of time that the VC-01 units were implanted will be summarized by Cohort, treatment group and overall, using the SAS. The summarization will include:

- Overall duration of exposure in days (calculated as [Date of explanation of last unit of any type] – [Date of implantation of first unit] + 1);
- Number of VC-01-DF units implanted;
- Duration of exposure in days of VC-01-DF units (calculated as [Date of explanation of last VC-01-DF unit] – [Date of implantation of first VC-01-DF unit] + 1);
- Number of sentinel units implanted;
- Duration of exposure in days of sentinel units (calculated as [Date of explanation of last sentinel unit] – [Date of implantation of first sentinel unit] + 1);
- Number of subjects with total planned number of units implanted and, if total not implanted, reason all units not implanted;
- Investigator's overall assessment of the implant surgical procedure;

- Number and percentage of subjects with a premature VC-01-DF unit explanted, and reason for premature explantation; and
- Number and percentage of subjects with a premature VC-01-DF unit explanted who remained in the study.

7.3.4 Demographics/Baseline Characteristics and Medical History

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 using the FAS.

Pertinent medical history will also be summarized similarly using the SAS. For medical history, all medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects with each medical condition and surgical procedure will be provided for each SOC and PT, by cohort and treatment group.

7.3.5 Prior and Concomitant Medications and Procedures

Concomitant medications will be categorized into medications given as part of surgical procedures and medications not given as part of surgical procedures. Diabetic medications will not be included.

Summarizations of prior and concomitant medications and procedures will be provided by Cohort and treatment group. The concomitant medications and procedures summary will be broken out separately for surgical and non-surgical medications (procedures will be considered non-surgical).

All medications will be coded using World Health Organization (WHO) drug classifications. The number and percent of safety subjects will be tabulated by Anatomical, Therapeutic, and Chemical (ATC) class and by preferred name.

7.3.6 Primary Analysis

Cohort 1 Primary Analysis

The FAS will be used for the histology summarizations, which include:

• The percentage of viable graft cells at post-implant time points relative to pre-clinical models. 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 are collected in the trial, it may inform that evaluation at additional time points is required.

• The percentage of graft cells staining positive for markers of beta cells at post-implant time points relative to pre-clinical models. The Sponsor will select appropriate biomarker staining to identify and quantify the amount of beta cells (e.g., insulin +, CHGA+, NKX6- 1+).

Histology results will be summarized by explant time point, anatomical location, and treatment group for Cohort 1.

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.

7.3.7 Secondary Analyses

7.3.7.1 Cohort 1 Secondary Analyses

For 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.
For the incidence of immune sensitization, any subject experiencing a confirmed sensitization will have an AE of 'sensitization' in the clinical study database. A listing will be provided for all subjects with a suspected event (the presence of donor anti-HLA antibodies absent prior to implant), with a column in the listing that indicates whether it is a confirmed immune sensitization (either confirmatory histological observations from at least one explanted unit and/or the presence of clinical symptoms; will have a corresponding 'sensitization' AE).

The number of Cohort 1 subjects experiencing off-target growth as evidenced by implanted VC-01 units via lumen ultrasound measurements (lumen thickness > 1 mm) *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.

For TEAEs, an overall summary will include the number and percentage of subjects experiencing:

- a TEAE;
- a TEAE by toxicity grade;
- a TEAE by relationship to VC-01 combination product;
- a TEAE by relationship to the surgical procedures required for VC-01 administration;
- a TEAE leading to study withdrawal;
- a treatment emergent SAE (TESAE);
- a TESAE by toxicity grade;

- a TESAE by relationship to VC-01 combination product;
- a TESAE by relationship to the surgical procedures required for VC-01 administration.

This overall summary table will include the number and percentage of subjects and also the total number of TEAE episodes. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table's total number of episodes.

Other AE tables that will be produced will include:

- A summary of subjects experiencing a TEAE by SOC and PT;
- A summary of subjects experiencing a TEAE by SOC, PT and toxicity grade;
- A summary of subjects experiencing a TEAE related to investigational product by SOC, PT;
- A summary of subjects experiencing a TEAE related to the surgical procedures required for VC-01 administration by SOC, PT;
- A summary of subjects experiencing a TESAE by SOC and PT;
- A summary of subjects experiencing a TESAE by SOC, PT and toxicity grade;
- A summary of subjects experiencing a TESAE related to investigational product by SOC, PT;
- A summary of subjects experiencing a TESAE related to the surgical procedures required for VC-01 administration by SOC, PT; and
- A summary of subjects experiencing a TEAE leading to study withdrawal by SOC and PT.

A listing of adverse events of special interest (AESIs) will also be provided.

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. 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 (separate from the overall explant 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.

Physical examination data will be listed by subject. *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.*

7.3.7.2 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. Change from baseline in safety data will also be summarized in a similar manner. Physical examination data will be listed by subject.

The number of Cohort 2 subjects experiencing off-target growth as evidenced by implanted VC-01 units via lumen ultrasound (lumen thickness > 1 mm) *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. For the incidence of immune sensitization, a listing will be provided for all subjects with a suspected event (the presence of donor anti-HLA antibodies absent prior to implant), with a column in the listing that indicates whether it is a confirmed immune sensitization (either confirmatory histological observations from at least one explanted unit and/or the presence of clinical symptoms; will have a corresponding 'sensitization' AE).

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 (separate from the overall explant listing)*, which includes the reason for explantation (i.e., safety issue, malfunction, damaged, planned explant, etc.).*

7.3.7.3 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 AUC0-2h following an MMTT and change from baseline to Week 52 in C-peptide AUC0-4h 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 ≤ 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).

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.

Change from baseline in frequency of hypoglycemic events (24-hour; daytime [start between 6 a.m. – 12 a.m.]; nocturnal [start between 12 a.m. – 6 a.m.]) at Weeks 16, 20, 26, 39, and 52 will each be analyzed using ANCOVA, with treatment group as a factor and the relevant baseline as a covariate. This analysis will be performed separately using HEs from the patient-reported diary and from CGM.

The number and percent of subjects free of severe hypoglycemic events between study visits (Weeks 16-20, Weeks 20-26, Weeks 26-39, Weeks 39-52, and Weeks 16-52) 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 time point, where appropriate). These analyses will be performed separately using HEs from patient-reported diary and HEs from CGM.

7.3.8 Cohort 2 Exploratory Analyses

In Cohort 2, the FAS will be used for the histology summarizations, which include 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; and histology results.

The percentage of viable graft cells at post-implant time points relative to pre-clinical models, summarized by treatment group and time point. The Sponsor may explant sentinel units beginning at the Week 4 time point. However, as data are collected in the trial, it will inform that evaluation at additional time points may be required.

The percentage of graft cells staining positive for markers of beta cells at post-implant time points relative to pre-clinical models, summarized by treatment group and time point. The Sponsor will select appropriate biomarker staining to identify and quantify the amount of beta cells (e.g., insulin +, CHGA+, NKX6-1+).

Histology results will be summarized by explant time point, anatomical location, and treatment group for Cohort 2.

8 Schedule of Assessments

Cohort 1 Schedule of Assessments

	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

	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)
Distribute Urine Sample Supplies for albumin/creatinine test (for next visit 1st morning void)	X									X		
ICD for Follow-Up Study[c]											X	
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 • HLA-PRA Class I & II Reactivity [e] • HLA-PRA Class 1 & II ID[f] 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												

	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)
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.												

Cohort 2 Schedule of Assessments

	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	

	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)
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	
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		

	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)
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 • HLA-PRA Class I & II Reactivity • HLA-PRA Class 1 & II ID[i] • 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.