An Open-Label, First-in-Human, Study Evaluating the Safety, Tolerability, and Efficacy of VC-02™ Combination Product in Subjects with Type 1 Diabetes Mellitus and Hypoglycemia Unawareness/
An Open-Label Study Evaluating the Safety and Tolerability of VC-02™ Combination Product in Subjects with Type 1 Diabetes Mellitus

Protocol Number:	VC02-101/102
Protocol Version:	VC02-101: 8.0 (Amendment #9) VC02-102: Canada: 3.0 (Amendment #2)
Protocol Date:	VC02-101: 18 May 2020 VC02-102: 27 April 2017

STATISTICAL ANALYSIS PLAN

Version 2.0

An Open-Label, First-in-Human, Study Evaluating the Safety, Tolerability, and Efficacy of VC-02™ Combination Product in Subjects with Type 1 Diabetes Mellitus and Hypoglycemia Unawareness/
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STATISTICAL ANALYSIS PLAN

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SAP Revisions

Version 1.0 of the SAP was finalized at the time of Protocol VC02-101 version 2.0 (28JUL2017) and Protocol VC02-102 (27APR2017). The following table details the changes made to the SAP due to subsequent protocol amendments.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
8.0 (Amendment #9) 18 May 2020	2.1.1	Removed "to Month 4" from the first bulleted study objective of VC02-101 Cohort 1 and VC02-102 Cohort 1.	Safety data is collected through Week 104. This language will be removed in subsequent protocol amendments.
8.0 (Amendment #9) 18 May 2020	2.2.1	Removed "to Month 4" from the Primary Endpoint of VC02-101 Cohort 1 and VC02-102 Cohort 1. Added "confirmed" to immune sensitization to third sub bullet within the VC02-101 and VC02-102 Primary Endpoint for Cohort 1. Revised definition of confirmed immune sensitization to include "confirmatory histological observations from at least one explanted unit and/or the presence of clinical symptoms" to third sub bullet within the VC02-101 and VC02-102 Primary Endpoint for Cohort 1.	Safety data is collected through Week 104. This language will be removed in subsequent protocol amendments. Language updated by Sponsor, and will be updated in subsequent protocol amendments. Language updated by Sponsor, and will be updated in subsequent protocol amendments.
8.0 (Amendment #9) 18 May 2020	2.2.2	Added "confirmed" to immune sensitization to the Safety and Tolerability Endpoints for VC02-101. Revised definition of confirmed immune sensitization to include "confirmatory histological observations from at least one explanted unit and/or the presence of clinical symptoms" to the Safety and Tolerability Endpoints for VC02-101.	Language updated by Sponsor, and will be updated in subsequent protocol amendments. Language updated by Sponsor, and will be updated in subsequent protocol amendments. Language updated by Sponsor, and

Protocol Version # Date	SAP Section	Modification	Description and Rationale
		Added Weeks 8, 12, 20, 65, and 91 to the first secondary efficacy endpoint for VC02-101.	will be updated in subsequent protocol amendments.
		Added study visit ranges for analysis to the secondary efficacy endpoint for VC02-101, "Percent of Subjects free of severe hypoglycemic events."	Language updated by Sponsor, and will be updated in subsequent protocol amendments.
		Added VC02-101 secondary endpoint "Percentage of subjects free of severe hypoglycemic events between Week 16 and Week 104 (or early termination)."	Language updated by Sponsor, and will be updated in subsequent protocol amendments.
		Removed "in the seven days preceding the Clinic Visits" from the VC02-101 secondary efficacy endpoint change from baseline in average daily insulin dose.	Language updated by Sponsor. The definition in SAP Section 4.6.5.1 reflects the new derivation for average daily insulin dose. This language will be updated in subsequent protocol amendments.
		Changed "dose" to "requirements" for the VC02-101 secondary efficacy endpoint "Percent of subjects who achieve 50% reduction in average weekly exogenous insulin requirements."	Language updated by Sponsor, and will be updated in subsequent protocol amendments.
		Changed the cut points in the VC02-101 secondary efficacy endpoint "Percent of time spent with blood glucose values at various cut points" to "54 mg/dL, ≥54 to <70 mg/dL, ≥70 mg/dL to ≤180 mg/dL, and >180 mg/dL)."	The secondary efficacy endpoint was changed in VC02-101 Protocol Version 8.0 (Amendment #9).
		Added ">250 mg/dL" as a cut point in the VC02-101 secondary efficacy endpoint "Percent of time spent with blood glucose values at various cut points	Language updated by Sponsor (follows ADA Guidelines). This language will be updated in subsequent protocol amendments.
		Added to the VC02-101	

Protocol Version # Date	SAP Section	Modification	Description and Rationale
		secondary efficacy endpoints, "Change from baseline to Weeks 16, 26, 39, 52, 78, and 104 in time-in-euglycemic range (≥70 mg/dL to ≤180 mg/dL), time-in-hypoglycemic ranges (<54 mg/dL and ≥54 to <70 mg/dL), and time-in-hyperglycemic ranges (>180 mg/dL) as measured by each subject's CGM." Added ">250 mg/dL" as a time-in-hyperglycemic range for the VC02-101 secondary efficacy endpoint change from baseline in time-in-hyperglycemic range.	The secondary efficacy endpoint was changed in VC02-101 Protocol Version 8.0 (Amendment #9). Language updated by Sponsor (follows ADA Guidelines). This language will be updated in subsequent protocol amendments.
8.0 (Amendment #9) 18 May 2020	3.1	Changed the number of implants per subject in VC02-101 to "twelve (12) units. Of the twelve implanted units, no more than four ten (104) will be VC-02-300 units, and the remainder will be VC-02-20 units. For example, if ten (10) VC-02-300 units are implanted, up to two (2) sentinels may also be implanted." Removed language about implants in VC02-102 subjects.	The number of implants was changed in VC02-101 Protocol Version 8.0 (Amendment #9). Only three subjects were enrolled in the VC02-102 study.
8.0 (Amendment #9) 18 May 2020	3.2.1	Changed the number of subjects enrolled in Cohort 2 from "40" to "60", and the total number of subjects enrolled to "75".	The number of implants was changed in VC02-101 Protocol Version 8.0 (Amendment #9).
8.0 (Amendment #9)	3.2.3	Updated description of the number of implants in VC02-101 Cohort 1 and Cohort 2 subjects,	The number of implants was changed in VC02-101 Protocol Version 8.0 (Amendment #9).

Protocol Version # Date	SAP Section	Modification	Description and Rationale
18 May 2020		the duration of the study, and the number of subjects enrolled in Cohort 2 as well as overall.	
8.0 (Amendment #9) 18 May 2020	4.2	Updated the definition of the FAS to exclude subjects enrolled in VC02-101 Cohort 1 or VC02-102 Cohort 1.	The FAS was updated in VC02-101 Protocol Version 8.0 (Amendment #9).
8.0 (Amendment #9) 18 May 2020	4.3	Updated the SAP Windows for the visits Week 104 and Week 105 (Follow-Up Visit).	The Week 104 visit did not need an upper range since it is the last visit of the study. The Week 105 (Follow-Up Visit) did not need SAP Windows.
8.0 (Amendment #9) 18 May 2020	4.4	Added analysis rules for dropouts and missing data for MMTTs and rules for determining TEAEs using missing or partial dates.	Clarified based on safety deliverables.
8.0 (Amendment #9) 18 May 2020	4.6.1	Updated derivations and visits for the analysis of the 2-hour MMTTs	The 2-hour MMTT visits were changed in VC02-101 Protocol Version 8.0 (Amendment #9).
8.0 (Amendment #9) 18 May 2020	4.6.2	Removed language pertaining to subjects who do not complete the 2-hour MMTT.	The C-peptide must be measurable to perform the analysis.
8.0 (Amendment #9) 18 May 2020	4.6.3	Updated the derivation for baseline average weekly frequencies of subject-reported HEs. Added statement "Data should not be used if an MMTT was performed on that day."	Clarified based interim safety summaries. The number of implants was changed in VC02-101 Protocol Version 8.0 (Amendment #9).
8.0 (Amendment #9)	4.6.4	Added section to include the derivation for the frequency of hypoglycemic events using CGM	The number of implants was changed in VC02-101 Protocol Version 8.0 (Amendment #9).

Protocol Version # Date	SAP Section	Modification	Description and Rationale
18 May 2020		data.	
8.0 (Amendment #9) 18 May 2020	4.6.5	Changed to Clarke Hypoglycemia Unawareness Score due to added SAP Section 4.6.4 Frequency of hypoglycemic events using CGM data.	N/A
8.0 (Amendment #9) 18 May 2020	4.6.6	Added Average exogenous daily insulin dose, average exogenous weekly insulin dose, and exogenous insulin independence due to the addition of SAP Section 4.6.4 Frequency of hypoglycemic events using CGM data.	N/A
8.0 (Amendment #9) 18 May 2020	4.6.6.1	Combined previous SAP Section 4.6.5.1 Daily and SAP Section 4.6.5.2 Weekly Exogenous Insulin Dose derivations. Updated derivations for Daily and Weekly Exogenous Insulin Dose.	N/A Clarified based on interim safety summaries.
8.0 (Amendment #9) 18 May 2020	4.6.6.2	Updated from previous SAP Section 4.6.5.3 and removed statement "Dates on exogenous daily insulin dose logs will be compared with clinic visit dates to derive which dates belong to the 7 days preceding clinic visits at Weeks 16, 26, 39, 52, 78, and 104, or belong to the 14 days preceding clinic visits at Weeks 16, 20, 26, 39, 52, 78, and 104."	Clarified based on interim safety summaries.
8.0 (Amendment #9) 18 May 2020	4.6.7	Updated from previous SAP Section 4.6.7. Updated cut points to "54 mg/dL, ≥54 to <70 mg/dL, ≥70 mg/dL to ≤180 mg/dL, and >180 mg/dL."	N/A The number of implants was changed in VC02-101 Protocol Version 8.0 (Amendment #9).

Protocol Version # Date	SAP Section	Modification	Description and Rationale
		Added cut point ">250 mg/dL".	Added by Sponsor, and will be updated in subsequent protocol amendments.
		Added statement: "Also, severe HEs characterized by an altered mental and/or physical status requiring assistance will be summarized."	Added by Sponsor, and will be updated in subsequent protocol amendments.
		Updated derivation of baseline CGM data and derivation post-baseline results.	Clarified based on interim safety summaries.
8.0 (Amendment #9) 18 May 2020	4.6.8	Updated from previous SAP Section 4.6.8.	N/A
		Removed scheduled visits for the 4-hour MMTT, 2-hour MMTT, and SOGCT tests.	Schedule Visits were updated in VC02-101 Protocol Version 8.0 (Amendment #9).
8.0 (Amendment #9) 18 May 2020	5.1	Combined Cohort 1 and Cohort 2 summaries into one bullet for the subjects that completed per protocol for both the FAS and SAS.	N/A
		Combined Cohort 1 and Cohort 2 summaries into one bullet for the subjects who withdrew prior to completing the study for both the FAS and SAS.	N/A
		Removed summaries for the status of subjects in Cohort 2 at Week 26 and Week 104.	Removed per Sponsor.
		Removed summaries for the number and percent of subjects in Cohort 1 and Cohort 2 who rolled over into the long-term follow-up study for both the FAS and SAS.	Data was not collected on subjects rolled over into the long-term follow-up study.

Protocol Version # Date	SAP Section	Modification	Description and Rationale
8.0 (Amendment #9) 18 May 2020	6.1	Removed language "for this Week 26 analysis, from only Cohort 2 [since Cohort 1 will not have Week 26 data]."	This language was duplicative.

8.0 (Amendment #9) 18 May 2020	6.2	Removed language "For time points up to and including Week 16, the FAS (both Cohort 1 and Cohort 2 subjects who meet the FAS criteria) will be used to analyze the secondary efficacy endpoints. For time points after Week 16, the FAS including only Cohort 2 subjects will be used to analyze the secondary efficacy endpoints."	This language was duplicative.
		Added Week 78 to the change from baseline in C-peptide $AUC_{0\text{-}4h}$ following an MMTT analysis.	This secondary efficacy endpoint was updated in VC02-101 Protocol Version 8.0 (Amendment #9).
		Added Week 8, 12, 20, 65, and 91 to the change from baseline in C-peptide AUC0-2h following an MMTT analysis.	Language updated by Sponsor, and will be updated in subsequent protocol amendments.
		Added language to the change from baseline in frequency of hypoglycemic events: "This analysis will be performed using HEs from both the patient-reported diary and from CGM. A listing of hypoglycemic events will be provided for both patient-reported data and from CGM data."	Clarified that the analyses would be based on two separate data types.
		Added the study visit ranges "(Weeks 16-20, Weeks 20-26, …, Weeks 91-104, and Weeks 16-104)" to the analysis of the number and percent of subjects free of severe hypoglycemic events.	Language updated by Sponsor, and will be updated in subsequent protocol amendments.
		Added the statement "These analyses will be performed using both HEs from patient-reported diary and HEs from CGM" to the analysis of the number and percent of subjects free of severe hypoglycemic events.	Clarified that the analyses would be based on two separate data types.
		Removed Week 20 from the	This secondary efficacy endpoint

Protocol Version # Date	SAP Section	Modification	Description and Rationale
		change from baseline in average daily insulin requirement analysis, and added Week 39. Added the cut points "54 mg/dL, ≥54 to <70 mg/dL, ≥70 mg/dL to ≤180 mg/dL, >180 mg/dL and >250 mg/dL" to the analysis of the percent of time spent with blood glucose values at various cut points.	was updated in VC02-101 Protocol Version 8.0 (Amendment #9). This secondary efficacy endpoint was updated in VC02-101 Protocol Version 8.0 (Amendment #9). The ">250 mg/dL" cut point was added by Sponsor, and will be updated in subsequent protocol amendments.
8.0 (Amendment #9) 18 May 2020	7.0	Added the confirmed immune sensitization definition.	Language updated by Sponsor, and will be updated in subsequent protocol amendments.
8.0 (Amendment #9) 18 May 2020	7.2	Added the reference to SAP Section 4.4 about the rules for determining TEAEs.	N/A
8.0 (Amendment #9) 18 May 2020	7.2.3	Updated definitions for the relationships "Not Related", "Possibly Related", and "Definitely Related". Added the definition for the combined category "Related".	The relationship definitions was changed in VC02-101 Protocol Version 8.0 (Amendment #9). Clarified for summaries described in SAP Section 7.2.5.
8.0 (Amendment #9) 18 May 2020	7.2.4	Updated definition of AESI.	The AESI definition was changed in VC02-101 Protocol Version 8.0 (Amendment #9).

Protocol Version # Date	SAP Section	Modification	Description and Rationale
8.0 (Amendment #9) 18 May 2020	7.2.5	Removed "highest" from toxicity summary tables. Removed "strongest" from relationship summary tables. Added summary tables for TEAEs and TESAEs by SOC, PT, and related to investigational product, surgical procedures required for VC-02 administration, and immunosuppressive drug regimen. Updated definition to summarize TEAEs by one episode per toxicity grade and causal relationship instead of the highest toxicity and strongest relationship.	Removed per Sponsor's request. Removed per Sponsor's request. Moved from previous SAP Section 7.6.1. Removed per Sponsor's request.
8.0 (Amendment #9) 18 May 2020	7.4	Removed BMI as data to be summarized in the vital signs table.	Removed per Sponsor's request.
8.0 (Amendment #9) 18 May 2020	7.6.1	Moved language re: causality related adverse events to SAP Section 7.2.5. Updated section to "Off-Target Growth".	N/A N/A
8.0 (Amendment #9) 18 May 2020	7.6.2	Updated to Immune Sensitization from previous SAP Section 7.6.3. Added definition of confirmed immune sensitization.	N/A
8.0 (Amendment #9) 18 May 2020	7.6.3	Updated to Implant Tolerability from previous SAP Section 7.6.4.	N/A

Protocol Version # Date	SAP Section	Modification	Description and Rationale
8.0 (Amendment #9) 18 May 2020	9.0	Added language "Quarterly during the first year of Cohort 2, and thereafter every three (3) to six (6) months until the last visit of the last Cohort 2 subject has occurred." Removed language about the DSMB meeting once every 12 weeks during enrollment of Cohort 2 and "After the last subject has enrolled in Cohort 2, the DSMB will meet every six (6) months until the last subject last visit has occurred. Additional meetings of the DSMB may be scheduled based on data review needs or by request."	The DSMB meeting description was changed in VC02-101 Protocol Version 8.0 (Amendment #9). The DSMB meeting description was changed in VC02-101 Protocol Version 8.0 (Amendment #9).
8.0 (Amendment #9) 18 May 2020	10.0	Updated the total number of subjects to be enrolled in Cohort 2 and overall. Added description of staggered enrollment and optimized device configuration and/or surgical implant technique.	The Sample Size and Power Calculation description was changed in VC02-101 Protocol Version 8.0 (Amendment #9). The Sample Size and Power Calculation description was changed in VC02-101 Protocol Version 8.0 (Amendment #9).
8.0 (Amendment #9) 18 May 2020	12.0	Update Schedule of Assessments	The Schedule of Assessments were changed in VC02-101 Protocol Version 8.0 (Amendment #9).

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
ATC	Anatomical, Therapeutic, and Chemical
ATG	Anti-Thymocyte Globulin
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CGM	Continuous Glucose Monitoring
CRO	Contract Research Organization
CV	Coefficient of Variation
DD	Delivery Device
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EoP2	End of Phase 2
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First-in-Human
FSH	Follicular Stimulating Hormone
GADA	Glutamate Decarboxylase Antibodies
GFR	Glomerular Filtration Rate
HbA1C	Hemoglobin A1C
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein Cholesterol
HE	Hypoglycemic Event
hESC	Human Embryonic Stem Cell
HIV	Human Immunodeficiency Virus
HLA-PRA	Human Leukocyte Antigen Panel Reactive Antibody
HU	Hypoglycemia Unawareness
IA-2A	Islet Antigen-2 Antibodies
IAA	Insulin Antibodies
ICD	Informed Consent Document
ITT	Intent-to-Treat
KM	Kaplan Meier
LDH	Lactate Dehydrogenase
LDL-C	Low Density Lipoprotein Cholesterol
LSM	Least Squared Method

Abbreviation	Definition
LST	Lymphocyte Stimulation Test
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MLR	Mixed Lymphocyte Reaction
MMTT	Mixed Meal Tolerance Test
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PEC	Pancreatic Endoderm Cells
PT	Preferred Term
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 Diabetes Mellitus
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
VC-02	VC-02™ Combination Product
VLDL	Very Low Density Lipoprotein
WBC	White Blood Cell
WHO	World Health Organization
ZnT8	Zinc Transporter 8

1. INTRODUCTION

This Phase 1/2, first-in-human clinical trial is comprised of two study protocols: VC02-101 and VC02-102. It will assess whether VC-02 can be implanted and maintained safely for up to two years in type 1 diabetes mellitus (T1DM) subjects with hypoglycemia unawareness (HU) in VC02-101, and for up to four months in otherwise healthy T1DM subjects in VC02-102. During the first three to six months, VC-02 is expected to vascularize adequately, and pancreatic progenitor cells are expected to differentiate into mature glucose-responsive, insulin-producing cells, capable of secreting insulin in response to serum glucose levels.

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

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

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

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

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

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

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

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

This document details the statistical methods planned to perform the interim and final analyses of Protocols VC02-101 and VC02-102.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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

VC02-101 Cohort 1 Study Objectives:

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

VC02-102 Cohort 1 Study Objectives:

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

VC02-101 Cohort 2 Study Objectives:

- Evaluate the clinical efficacy and further assess safety and tolerability of VC-02 combination product from implantation to Month 24.
- Explore effects of weight, gender, body mass index (BMI), or other potentially interacting factors on the responsiveness of the subjects to the experimental intervention.

2.1.2 Exploratory Objectives

VC02-101 and VC02-102 - Cohort 1 and 2 Study Objectives:

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

2.2 Endpoints

2.2.1 Primary Endpoint

VC02-101 and VC02-102 Primary Endpoint / Cohort 1:

- Targeted safety and tolerability profile, inclusive of:
  - The incidence of adverse events (AEs) with causality related to VC-02 combination product, the surgical procedures required for VC-02 administration, and the immunosuppressive drug regimen.
  - The incidence of off-target growth as evidenced by implanted VC-02 units via lumen ultrasound measurements, or by histological examination of explants.
  - The incidence of confirmed immune sensitization defined by presence of donor anti-human leukocyte antigen (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) for up to four hours post-implantation and at subsequent visits.

VC02-101 Primary Endpoint / Cohort 2:

- 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).

2.2.2 Secondary Endpoints

Secondary Safety and Tolerability Endpoints:

VC02-101:

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

- All reported AEs
    - The incidence of confirmed 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) for up to four hours post-implantation and at subsequent visits.
- The incidence of subjects requiring a premature explant due to safety, tolerability, or malfunction issues.

VC02-102:

The comprehensive safety profile of VC-02 combination product implanted for up to four months as measured by:

- All reported AEs
- The incidence of subjects requiring a premature explant due to safety, tolerability, or malfunction issues.

Secondary Efficacy Endpoints:

VC02-101:

- Change from baseline to Weeks 8, 12, 16, 20, 26, 39, 52, 65, 78, 91, and 104 in C-peptide area under the curve from 0 to 2 hours ($AUC_{0\text{-}2h}$) or $AUC_{0\text{-}4h}$ following an MMTT;
- Time to onset of biological response of C-peptide following MMTT;
- Percent of subjects achieving a positive stimulated C-peptide (defined as >0.2 ng/mL) after implant;
- Change from baseline to Weeks 16, 26, 39, 52, 78, 104 in weekly frequency of hypoglycemic events;
- Percent of subjects free of severe hypoglycemic events between study visits starting with Week 16 (i.e., Weeks 16-20, Weeks 20-26, Week 26-39, Weeks 39-52, Weeks 52-65, Weeks 65-78, Weeks 78-91, Weeks 91-104);
- Percentage of subjects free of severe hypoglycemic events between Week 16 and Week 104 (or early termination).
- Change from baseline to Weeks 16, 26, 39, 52, 78 and 104 in Clarke score;

- Change from baseline to Weeks 16, 26, 39, 52, 78, and 104 in average daily insulin dose;
- Percent of subjects who achieve a 50% reduction in average weekly exogenous insulin requirements from baseline to Weeks 16, 20, 26, 39, 52, 78, and 104;
- Percent of subjects who achieve exogenous insulin independence;
- 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 monitoring (CGM) device.
- Change from baseline to Weeks 16, 26, 39, 52,78, and 104 in time-in-euglycemic range (≥70 mg/dL to ≤180 mg/dL), time-in-hypoglycemic ranges (<54 mg/dL and ≥54 to <70 mg/dL), and time-in-hyperglycemic ranges (>180 mg/dL and > 250 mg/dL) as measured by each subject's CGM.

2.2.3 Exploratory Endpoints

VC02-101 and VC02-102 Exploratory Endpoints/ Cohort 1 and 2:

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

3. INVESTIGATIONAL PLAN

3.1 Study Design

This Phase 1/2, first-in-human clinical trial is comprised of two study protocols: VC02-101 and VC02-102.

The VC02-101 study will be an open-label, FIH, clinical trial in subjects with T1DM and HU. Two cohorts are planned for enrollment in this trial, with enrollment of Cohort 1 occurring prior to enrollment of Cohort 2.

All VC02-101 enrolled subjects will have up to one or more VC-02-300 units and/or one or more smaller VC-02-20 (sentinel) units implanted in anatomical locations involving the trunk or extremities (e.g., back, flanks, arms, legs, and abdomen) suitable for implantation, as deemed appropriate by the Investigator and/or Surgeon after consultation with the Sponsor. Documentation of the implant plan for a subject will be provided to the Investigator by the Sponsor. Implantation will be executed under an anesthetic with or without sedation. The following are the maximum units that can be implanted per cohort:

- In Cohort 1, subjects are implanted with up to two (2) VC-02-300 units and up to six (6) sentinels; or up to ten (10) sentinels only.
- In Cohort 2, subjects are implanted with up to twelve (12) units. Of the twelve implanted units, no more than ten (10) will be VC-02-300 units, and the remainder will be VC-02-20 units. For example, if ten (10) VC-02-300 units are implanted, up to two (2) sentinels may also be implanted.

The VC02-102 study will be an open-label clinical trial in otherwise healthy subjects with T1DM. All subjects enrolled in Protocol VC02-102 are considered part of Cohort 1 for analysis purposes.

3.2 Treatment

3.2.1 Randomization Scheme and Treatment Arm Assignment

There is no randomization scheme for this study. Subjects will be summarized by cohort and treatment group (the number of initially implanted VC-02-300 units). If, during the study, the number of sentinels implanted in subjects who do not have VC-02-300 units varies widely (e.g., one subject has one sentinel unit implanted while another subject has 10 sentinel units implanted), the "zero VC-02-300 unit" treatment group may be further broken out by the number of sentinels implanted.

A minimum of three (3) and up to 15 subjects total will be enrolled in Cohort 1 at one (1) or more sites. Cohort 2 will enroll up to 60 subjects from up to ten (10) sites. Therefore, the total enrollment possible for the trial (Cohort 1 and Cohort 2) is up to 75 subjects.

3.2.2 Blinding

There is no blinding since this study is open-label.

3.2.3 Dosing Schedule

VC02-101 and VC02-102 Cohort 1:

At a minimum, the first three (3) subjects in Cohort 1 will be enrolled sequentially in order to assess safety and tolerability data thru Week 2 before implanting the next subject. For example, data thru Week 2 from the first subject will be formally reviewed by the Sponsor prior to allowing the Investigator to implant the next subject. If a treatment-related serious adverse event (SAE) is observed within the first two weeks in the subject, the implantation of the next subject will be postponed until consultation between the Sponsor and Investigator has devised appropriate safeguards. Overall, if no treatment-related SAEs are observed with the first three (3) subjects after each has reached Week 4, additional Cohort 1 enrollment may then be performed in parallel.

Initially, up to six sentinels will be implanted in the first three (3) Cohort 1 subjects in order to provide sufficient histologic data to assess preliminary safety and tolerability. The first three (3) subjects enrolled in Cohort 1 will not be implanted with VC-02-300 units. After the first three subjects are enrolled in Cohort 1 and initial safety and tolerability is confirmed, VC-02-300 units may then be implanted in subsequent, enrolled subjects and the stimulated C-peptide levels will be monitored. These additional Cohort 1 subjects may be implanted with up to two (2) VC-02-300 units and up to six (6) VC-02 sentinels total. The decision as to the number of VC-02-300 units implanted in subsequent subjects will be data-driven and this number may be reduced. However, if no VC-02-300 units are implanted in these additional; Cohort 1 subjects, up to ten (10) VC-02 sentinels may instead be implanted. No subjects enrolled in VC02-102 will receive VC-02 300 units and will have up to six smaller, VC-02-20 (sentinel) units implanted in anatomical locations involving the trunk or extremities (e.g., back, flanks, arms, legs, and abdomen) suitable for implantation, as deemed appropriate by the Investigator and/or Surgeon after consultation with the Sponsor. Documentation of the implant plan for a subject will be provided to the Investigator by the Sponsor. Implantation will be executed under an anesthetic with or without sedation.

The total duration of treatment (implantation) may be up to two (2) years for each VC02-101

Cohort 1 subject. Sentinels and/or VC-02-300 units may be explanted at various time points post-implant to assess the status of cell viability and differentiation, vascularization, and the host response. Including the requirements of the screening period, Cohort 1 subjects will complete a total of 18 study visits spanning approximately 25 months. The total duration of treatment (implantation) may be up to four (4) months for each VC02-102 Cohort 1 subject. Sentinels may be explanted at various time points post-implant to assess the status of cell viability and differentiation, vascularization, and the host response. Any remaining units will be explanted at Week 16 (four months).

At the end of the treatment period for each subject enrolled under the VC02-101 and VC02-102 protocols, all remaining implanted units will be removed, and the subject will be required to participate in a separate, one-year, follow-up, non-interventional, observational study. The primary purpose of this additional study is to ensure there are no long-term safety issues associated with previous implantation with VC-02.

Figure 1: VC02-101 Cohort 1 Study Schematic

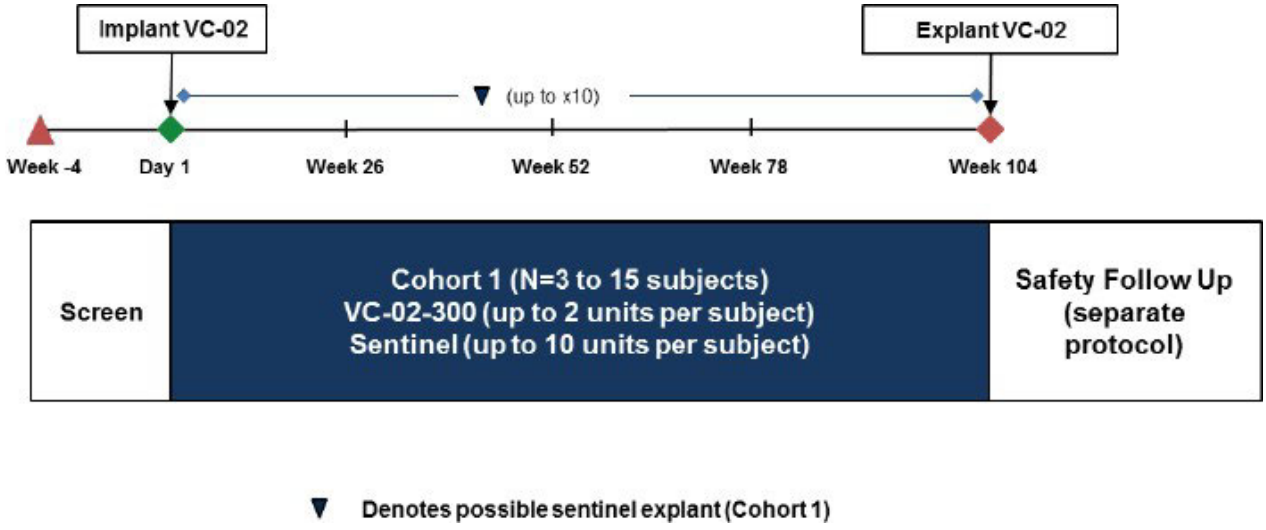
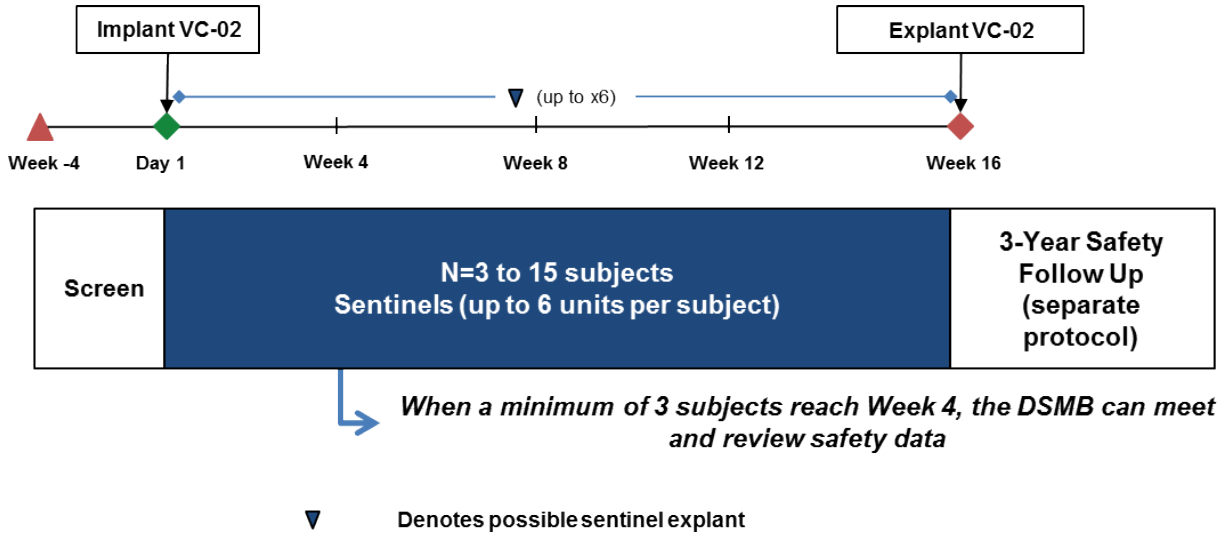


Figure 2: VC02-102 Cohort 1 Study Schematic



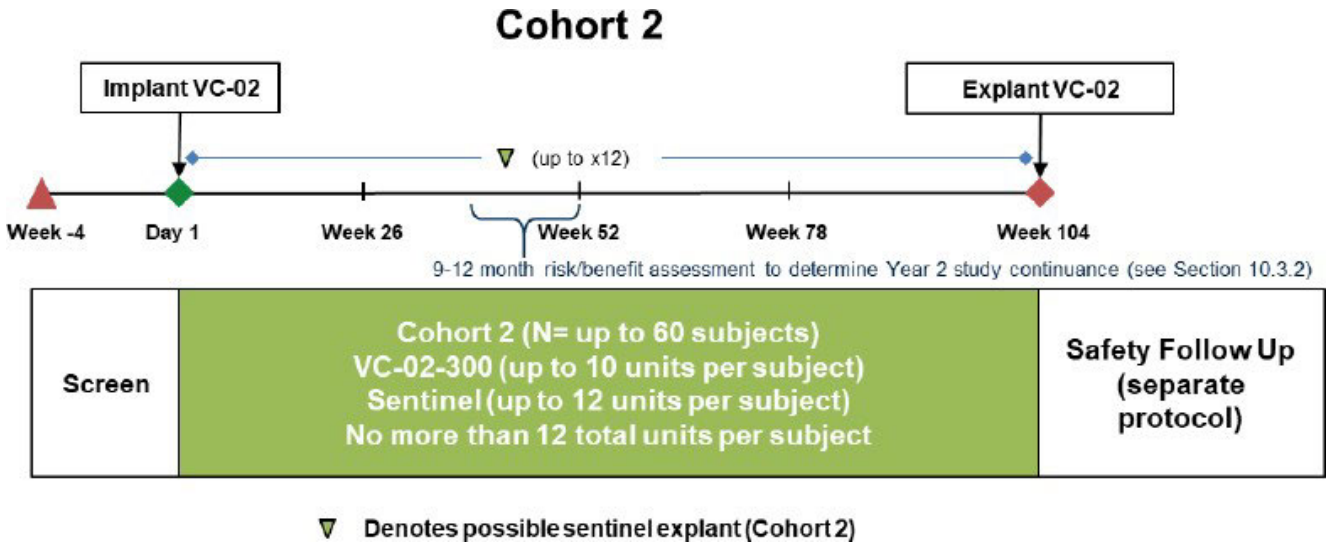
VC02-101 Cohort 2:

Enrollment of Cohort 2 will include up to 60 additional subjects who will be implanted with up to twelve units. Of the twelve implanted units, no more than ten (10) will be VC-02-300 units and the remainder will be VC-02-20, sentinel units. For example, if ten (10) VC-02-300 units are implanted, up to two (2) sentinels may also be implanted. The total duration of treatment may be up to two (2) years for each Cohort 2 subject. Sentinels and/or VC-02-300 units may also be explanted at various time points post-implant, but the Sponsor generally intends to explant sentinels at later time points (e.g., Week 12 or beyond) and to allow VC-02-300 units to remain implanted for the entire study duration. All remaining VC-02-300 and sentinel units will be explanted at Visit 17/Week 104.

The number of VC-02-300 units to be implanted in Cohort 2 subjects will be a data-driven decision and may vary between subjects. The Sponsor will review available C-peptide results from Cohort 1 subjects, as well as an ongoing review of C-peptide results from implanted Cohort 2 subjects, to determine the optimal number of VC-02-300 units to implant in subsequent subjects. The Sponsor generally intends to implant the least number of VC-02-300 units required to provide the intended therapeutic benefit.

There is no Cohort 2 in VC02-102.

Figure 3: VC02-101 Cohort 2 Study Schematic



3.2.4 Subject Compliance

Subjects who are withdrawn prematurely from the study will have the VC-02-300 units (if applicable) and sentinels explanted. If a subject withdraws from the trial and also withdraws consent for disclosure of future information in writing, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before withdrawal of consent.

Subjects who have not withdrawn consent, but who have been discontinued from the main study prematurely (with products explanted) will be rolled over into a 1-year, long-term, follow-up trial.

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

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

The phrase "treatment group" is used in this section to denote the number of initially implanted VC-02-300 units. If a subject has a VC-02-300 unit explanted for any reason and remains in the study, then he/she will be included in the treatment group that is described by the number of VC-02-300 units originally implanted. If no VC-02-300 units are implanted, but sentinel units are implanted, then the subject will be included in the "0 implanted VC-02-300 units" treatment group. If, during the study, the number of sentinels implanted in subjects who do not have VC-02-300 units varies widely (e.g., one subject has one sentinel unit implanted while another subject has 10 sentinel units implanted), the "zero VC-02-300 unit" treatment group may be further broken out by the number of sentinels implanted.

As the VC02-101 and VC02-102 studies collectively represent the first-in-human trial, there are no statistical hypotheses regarding treatment effects. Rather, displays and comparisons of study results – regarding safety and efficacy among the treatment groups – will primarily utilize descriptive statistics, as noted below.

Unless otherwise specified, continuous variables will be summarized by presenting the number of

non-missing observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by presenting the number of subjects and percentage for each category.

Summary results will be provided for each cohort and treatment group as well as overall.

All tabulations will be based on pooled data across centers.

Analyses will be performed using SAS for Windows statistical software, version 9.4 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

CTI Clinical Trial and Consulting Services will perform all efficacy and safety statistical analyses.

Subject data will be listed, sorted by protocol, cohort, treatment group (number of VC02-300 units and ascending VC02-20/sentinel units [if applicable]), and subject number.

4.1 Data Quality Assurance

ViaCyte Inc., or its designated representative, will conduct a pre-study visit for each study site to verify the qualifications of the investigator, inspect study site facilities, become familiarized with site staff assigned to the study, and inform the investigator of responsibilities and procedures for ensuring correct study documentation.

Data may be pulled by CTI Biostatistics for Data Safety Monitoring Board (DSMB) or interim analysis at a time when source verification and query resolution is ongoing.

All SAS programs used to create analysis datasets and output will be validated by ensuring that the ".log" files are void of all errors, warnings and notes indicative of problems. Additionally, each program will be checked to ensure that it performs according to the program specification. All programs are developed and validated by separate members of the CTI Biostatistics Department.

4.2 Analysis Sets

The Full Analysis Set (FAS) is the intent-to-treat (ITT) set of subjects. This set is defined as all subjects who were enrolled into VC02-101 and received implantation of at least one VC-02-300 or sentinel unit on Study Day 1. Note that Cohort 1 in VC02-101 and in VC02-102 have no efficacy endpoints, so the subjects from Cohort 1 in VC02-101 and VC02-102 are not included in the FAS. All Cohort 2 VC02-101 efficacy summaries/analyses will be performed on the FAS. Subjects will be summarized by treatment group.

The Safety Analysis Set (SAS) will include all subjects from Cohort 1 and Cohort 2 who were enrolled into VC02-101 or VC02-102 and in whom an implant surgery was attempted, regardless of whether any VC-02-300 units or sentinel-sized units were actually implanted. The SAS will be used for safety summaries. All subjects enrolled in Protocol VC02-102 are part of Cohort 1.

4.3 Assessment 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 procedure for VC-02-300 and/or sentinel unit implantation was attempted.

Study visits will have windows as per the following schema:

Study Visit	*Target Study Day of Visit*	*SAP Windows*
Scheduled Study Visits for Cohort 1 and Cohort 2		
Week -4	-29	Day -36 to Day -23
Week -3	-22	Day -22 to Day -1
Day 1	1	Day 1
Day 2	2	Day 2 to Day 3
Week 2	15	Day 4 to Day 21
Week 4	29	Day 22 to Day 42
Week 8	57	Day 43 to Day 70
Week 12	85	Day 71 to Day 98
Week 16 (Cohort 1 Only)	113	Day 99 to Day 117
Week 16 (Cohort 2 Only)	113	Day 99 to Day 126
Week 17 (Follow-Up Visit: Cohort 1 Only)	120	Day 118 to Day 118+
Scheduled Study Visits for Cohort 2 Only		
Week 20	141	Day 127 to Day 161
Week 26	183	Day 162 to Day 228
Week 39	274	Day 229 to Day 319
Week 52	365	Day 320 to Day 410
Week 65	456	Day 411 to Day 501
Week 78	547	Day 502 to Day 592
Week 91	638	Day 593 to Day 683
Week 104	729	Day 684 to ∞
Week 105 (Follow-Up Visit)	Last Date of Explantation + 7 Days	Not applicable

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 is 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. ViaCyte will be notified of Study Visits that are not within the Study Visit Statistical Analysis Plan (SAP) windows. Data collected as an unscheduled visit will be re-assigned to a Study Visit based on the SAP visit windows specified.

Baseline will be defined as the last non-missing value prior to the start time of the surgical procedure for VC-02-300 and/or sentinel unit implantation, unless otherwise specified.

If more than one assessment exists within a single visit window (i.e., vital signs, laboratory samples, etc.), then the value taken closest to the target day of that visit will be used for analysis and summary purposes. In cases where two assessments are equally close to the target day, then

the first value will be used for analysis. Data from all assessments will be provided in the listing.

4.4 Handling of Dropouts or Missing Data

MMTTs 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. The 0 minute timepoint will be imputed as zero (the value '0').

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 AE dates where the start and/or end date are partial dates, the following rules will apply:

- If a month and year of an event is clearly after implant, then the dates will remain partial dates but the AEs will be indicated as treatment-emergent.
- For partial dates within the same month and year as the implant, if the site knows the event occurred prior to implant, then they enter "01" for the day. If the site knows the event occurred after implant, then they enter the last day of the month. Using these rules, the AEs will be correctly indicated as treatment-emergent or non-treatment-emergent.

For partial dates within the same month and year as the implant, if the site does not know whether the event occurred prior to the implant, then they will be instructed to make their best estimate. For partial dates entered prior to this instruction being added to the eCRF guidelines, "01" will be imputed for the day, which will result in all such AEs being indicated as treatment-emergent.

No additional imputations will be performed for any other missing data in this study.

4.5 Multiple Comparisons

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

4.6 Data Derivations and Transformations

All data derivations are for efficacy data. Therefore, information in this section pertain only to Protocol VC02-101.

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

Area under the curve (AUC) 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,

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

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

After Implantation Visit 3, 2-hour MMTTs will be conducted at Visit 7 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 12 (Week 39), Visit 14 (Week 65), and Visit 16 (Week 91). After Implantation Visit 3, 4-hour MMTTs will be conducted at Visit 11 (Week 26), Visit 13 (Week 52), Visit 15 (Week 78) and Visit 17 (Week 104 or Early Termination). For subjects with an immeasurable C-peptide (≤0.1 ng/mL) as determined by the simplified oral glucose challenge test, the AUC of the respective 2-hour MMTT will be set to 0. 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 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 4.4 will be applied.

Baseline 4-hour MMTT is defined as the 4-hour MMTT performed during the Screening period. Similarly, baseline 2-hour MMTT is defined as the 2-hour MMTT (the first 2 hours) from the 4-hour MMTT performed during the Screening period.

4.6.2 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. 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.

4.6.3 Frequency of hypoglycemic events using subject-reported diary data

HE data collected on the "Hypoglycemic Event" eCRF page will be used collectively for HE data summary and analysis. These data are collected from the subject-completed diaries. Hypoglycemic event logs will be completed via subject diary (via provisioned phones) by subjects. Investigators will review the hypoglycemic event logs completed by the subjects at each study visit. Blank values in the hypoglycemic events (HEs) log are considered to be 0 values.

HEs will be classified in six ways: total HEs, severe HEs, 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. Severe HEs (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. to 12 a.m. period. Severe daytime HEs are SHEs that start during the 6 a.m. to 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 -3 (i.e., the day prior to immunosuppression induction) and working backwards for up to 28 days (through Day -30). For instances in which the available pre-implant dataset provides <28 days of data, the dataset will be supplemented with post-implant data, using data from Day 4 forward until 28 days of data is available. Data from days on which an MMTT or SOGCT 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 (the actual study visit at Weeks 16, 26, 39, 52, 78, and 104) 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. For example, the total number of HEs, SHEs, nocturnal HEs, severe nocturnal HEs, daytime HEs, and severe daytime HEs occurring in the 14 calendar days prior to the Week 16 visit 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 Week 16. Data should not be used if an MMTT was performed on that day.

4.6.4 Frequency of hypoglycemic events using CGM data

CGM will also 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 -3 (i.e., the day prior to immunosuppression induction) and working backwards for up to 28 days (through Day -30). For instances in which the available pre-implant dataset provides <28 days of data, the dataset will be supplemented with post-implant data, using data from Day 4 forward until 28 days of data is available. Data from days on which an MMTT or SOGCT was performed, will not be included in the calculation. 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. Data should not be used if an MMTT or SOGCT was performed on that day.

4.6.5 Clarke Hypoglycemia Unawareness Score

There is no data derivation for the Clarke Hypoglycemia Unawareness Score (the data is collected on the eCRF, and no derivation is required).

4.6.6 Average exogenous daily insulin dose, average exogenous weekly insulin dose, and exogenous insulin independence

Determination of exogenous insulin dosage levels and exogenous insulin independence will be determined based on the subjects' Patient Cloud recordings and not based on the investigator's case report form (eCRF) entries.

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

Exogenous daily insulin dose logs will be completed via subject diary (via provisioned phones) by subjects. Investigators will review the exogenous insulin dose logs completed by the subjects at each study visit.

4.6.6.1 Daily and Weekly Exogenous Insulin Dose

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 -3 (i.e., the day prior to immunosuppression induction) and working backwards for up to 28 days (through Day -30). For instances in which the available pre-implant dataset provides <28 days of data, the dataset will be supplemented with post-implant data, using data from Day 4 forward until 28 days of data is available. Data from days on which an MMTT or SOGCT was performed, will not be included in the calculation.

At Weeks 16, 26, 39, 52, 78, and 104, the last 7 daily total exogenous insulin doses recorded in the log will be used to calculate the average daily and the average 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 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).

In each period, subjects must have four different days with recorded exogenous insulin doses in order for the value to be calculated.

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.

4.6.6.2 Exogenous Insulin Independence

Exogenous insulin independence will be defined in two ways.

First, achieving exogenous insulin independence is 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. Missing or blank values on the daily 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.

4.6.7 Percent of time spent with blood glucose values at various cut points

Subjects in Cohort 2 of Study VC-02-101 are required to wear their CGM, at minimum, during the 30-day period prior to their scheduled clinic visits, although wearing of the CGM for the entire two-year study is encouraged. The 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. Also, severe HEs characterized by an altered mental and/or physical status requiring assistance will be summarized.

The summarization 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 12 a.m. – 6 a.m.) time period.

Baseline CGM data will be utilized to calculate percentages spent with blood glucose values at the various cut points for up to 28 days, starting at Day -3 (i.e., the day prior to immunosuppression induction) and working backwards for up to 28 days (through Day -30). For instances in which the available pre-implant dataset provides <28 days of data, the dataset will be supplemented with post-implant data, using data from Day 4 forward until 28 days of data is available. Data should not be used if an MMTT or SOGCT was performed on that day. 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.

4.6.8 Early termination (ET) visit mapping

For safety assessments, including clinical laboratory assessments, vital signs, electrocardiogram (ECG), and physical examination, the ET visit will not be mapped. The ET data will be combined

with Week 104 data for summaries, and the time point will be displayed as "Week104/ET".

For the efficacy assessment MMTT and Clark Hypoglycemia Unawareness Score, the ET visit will be mapped to the next scheduled visit at which that data type is collected. This mapped scheduled visit data will be used for analyses and summaries.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The following will be summarized in the disposition table:

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

These summaries will be tabulated within cohort and treatment group as well as overall.

5.2 Protocol Deviations

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

5.3 Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize the demographic and baseline characteristics (age, gender, race, ethnicity, baseline vital signs, and pertinent medical history) for the SAS, by cohort and treatment group.

5.4 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 presented for each SOC and PT for the SAS, by cohort and treatment group.

5.5 Prior and Concomitant Medications

Concomitant medications will be categorized into either non-immunosuppressant medications, immunosuppressant medications, or medications given as part of surgical procedures. Summaries of each category will be presented separately. Diabetic medications will not be included.

All prior and concomitant medication data will be listed, sorted by treatment group, then

investigative site and subject number, start and stop date. Information listed will include medication, indication, dose, frequency and route of administration.

For VC02-102, all doses of insulin will be listed, sorted by treatment group, then investigative site and subject number, and date of administration. Information listed will include type of insulin and total units taken for the entire day.

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.

6. EFFICACY ANALYSIS

All efficacy summaries/analyses will be performed on the VC02-101 FAS. Subjects will be summarized by cohort and treatment group.

6.1 Primary Efficacy Endpoint and Analysis

Primary Endpoint / Cohort 2:

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

A listing of the 4-hr MMTT/C-Peptide and Glucose results will be provided.

6.2 Secondary Efficacy Endpoints and 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.

For all secondary efficacy analyses, the FAS (Cohort 2 subjects who meet the FAS criteria) will be used. Change from baseline in C-peptide $AUC_{0\text{-}4h}$ following an MMTT at Weeks 52, 78, and 104 and change from baseline in C-peptide $AUC_{0\text{-}2h}$ following an MMTT at Weeks 8, 12, 16, 20, 39, 52, 65, 78, 91, and 104 will be analyzed in a similar manner to the ANCOVA performed for change from baseline in C-peptide $AUC_{0\text{-}4h}$ at Week 26, with the relevant baseline as the covariate. For subjects who continue to have a C-peptide ≤0.1 ng/mL as determined by the simplified oral glucose challenge test, the AUC of the respective 2-hour MMTT will be set to 0. A listing of the 2-hr MMTT/C-Peptide and Glucose results will be provided, as well as a listing of the simplified oral glucose challenge.

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

The number and percent of subjects achieving a positive stimulated C-peptide (defined as > 0.2 ng/mL) after implant will 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).

Change from baseline in frequency of hypoglycemic events (24-hour; daytime [start between 6 a.m. – 12 a.m.]; nocturnal [start between 12 a.m. – 6 a.m.]) at Weeks 16, 26, 52, 78 will be analyzed using ANCOVA, with treatment group as a factor and the relevant baseline as a covariate. This analysis will be performed using HEs from both the patient-reported diary and from CGM. A listing of hypoglycemic events will be provided for both patient-reported data and from CGM data.

The number and percent of subjects free of severe hypoglycemic events between study visits (Weeks 16-20, Weeks 20-26, …, Weeks 91-104, and Weeks 16-104) will each be analyzed using Fisher's exact test. The number and percent of subjects in each treatment group and the p-value from the Fisher's test will be provided (at each time point, where appropriate). These analyses will be performed using both HEs from patient-reported diary and HEs from CGM.

Change from baseline to Weeks 16, 26, 52, 78 and 104 in Clarke score will be analyzed using ANCOVA, with treatment group as a factor and the relevant baseline as a covariate. A listing of the Clarke total score will be provided.

Change from baseline to Weeks 16, 26, 39, 52, 78 and 104 in average daily insulin requirement in the seven days preceding the clinic visit will be analyzed using ANCOVA, with treatment group as a factor and the relevant baseline as a covariate. A listing of insulin dosing will be provided.

The number and percent of subjects who achieve a 50% reduction in average weekly exogenous insulin dose from baseline to Weeks 16, 20, 26, 39, 52, 78, and 104 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).

The number and percent of subjects who achieve exogenous insulin independence (both definitions 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).

Percent of time spent with blood glucose values at various cut points at each scheduled visit will be summarized descriptively. The coefficient of variation (CV) of blood glucose values will be included in the summary. 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. The number of subjects with Prolonged HEs (duration > 120 minutes for cut points ≤54 mg/dL and ≤70 mg/dL) will also be summarized.

6.3 Pharmacokinetic and Pharmacodynamic Analyses

There will be no pharmacokinetic or pharmacodynamics testing done in this study.

7. SAFETY ANALYSIS

Unless otherwise specified, the VC02-101 and VC02-102 SAS (both Cohort 1 and Cohort 2 subjects who meet the SAS criteria) will be used for the primary safety summarizations. Other safety data, such as vital signs and clinical laboratory data will be summarized by study visit and treatment group. Where appropriate, change from baseline in safety data will also be summarized in a similar manner.

For the secondary safety endpoint of confirmed immune sensitization defined by presence of donor anti-HLA antibodies absent prior to implant with either confirmatory histological observations

from at least one explanted unit and/or the presence of clinical symptoms will have all relevant data described in a clinical narrative. In addition, data of interest from the assays may be summarized by cohort and treatment group as well as overall.

7.1 Extent of Exposure

The following information will be summarized using descriptive statistics by cohort and treatment group as well as overall:

- Overall duration of exposure (days), calculated as (Date of explantation of last unit of any type - Date of implantation of first unit +1)
- Number of VC-02-300 units implanted
- Duration of exposure (days) of VC-02-300 units, calculated as (Date of the last VC-02-300 explantation – Date of first VC-02-300 unit implantation + 1)
- Number of VC-02-20 units implanted
- Duration of exposure (days) of VC-02-20 units, calculated as (Date of the last VC-02-20 explantation – Date of first VC-02-20 unit implantation + 1)
- The number of subjects with total planned number of units implanted. If total planned number of units not implanted, then summarize the reason all units not implanted
- Investigator's overall assessment of the implant surgical procedure
- The number and percentage of subjects with a premature explantation of a VC-02-300 unit
- The number and percentage of subjects with a premature explanation of a VC-02-300 unit who remained in the study
- Reason for premature explantation of a VC-02-300 unit

A listing of implantation and explantation information as well as a separate listing containing investigational product incision information will also be provided.

7.2 Adverse Events

All AEs with a start date occurring between Visit 2 (Week -3) and through the subject's last visit must be recorded. At the conclusion of the trial, any ongoing AEs will be followed until at least 28 days after the final explantation procedure to determine the final reported outcome of the event.

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

The reporting period for AEs and SAEs may overlap with the timing of the subject's participation in the mandatory, 1-year follow-up study. Further details on how to report ongoing AEs spanning the period between the VC02-101 or VC02-102 protocols and follow-up study will be outlined in the separate follow-up protocol.

For this study, missing or partial AE start and/or stop dates will not be imputed using statistical programming. However, rules for determining if an AE is treatment-emergent or non-treatment-

emergent will be used for partial dates; these rules are discussed in Section 4.4 of this SAP.

7.2.1 Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an AE that starts on or after the date of implant surgery.

7.2.2 Adverse Event Toxicity Grade

The Investigator will use the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE v4.0.3) guidelines to describe the maximum intensity of the AE. For purposes of consistency, these toxicity 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.

7.2.3 Causality Assessment of Adverse Events

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

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

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

Relationship of an AE to VC-02, the surgical procedures, and the immunosuppression drugs will be assessed as follows:

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

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

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

The combined category of "related" AEs to investigational product exposure, surgical procedures, or the immunosuppression drugs, will include those events that are Unlikely Related, Possibly Related, Definitely Related.

7.2.4 Adverse Events of Special Interest (AESI)

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

- AEs leading to the unexpected or premature explantation of VC-02-300 or sentinel units.
- AEs that result in early withdrawal from the study.
- Severe hypoglycemic events occurring after VC-02 implantation possibly or definitely related to VC-02.

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

7.2.5 Serious Adverse Events

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, 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 HE eCRF.

7.2.6 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.

Because of the limited shelf-life of the investigational product, the results of the 14-day sterility testing of VC-02 are not available until after implantation occurs. In the unexpected event of positive culture results from this test, the Sponsor will notify the Investigator, who will then notify the subject. The Sponsor will initiate further testing of the positive sample to identify the microorganism and conduct a root-cause analysis. The Investigator and Sponsor will evaluate any additional actions required to appropriately monitor the subject based on the results of the sample. If the medical condition of the subject is impacted as a consequence of the microorganism causing the positive sterility results, the event should be reported as a SUSAR.

7.2.7 Adverse Event Summaries

All AEs (serious and nonserious) occurring after completion of the informed consent process and before the end of study, regardless of relationship to study drug, will be included and classified by SOC and PT using MedDRA.

For TEAEs, the following will be summarized and presented for the SAS:

i. An overall summary of TEAEs, which includes:
   a. the number and percentage of subjects experiencing a TEAE
   b. the number and percentage of subjects experiencing a TEAE by toxicity grade
   c. the number and percentage of subjects experiencing a TEAE by relationship to VC-02 combination product
   d. the number and percentage of subjects experiencing a TEAE by relationship to the surgical procedures required for VC-02 administration
   e. the number and percentage of subjects experiencing a TEAE by relationship to the immunosuppressive drug regimen
   f. the number and percentage of subjects experiencing a TEAE leading to study withdrawal
   g. the number and percentage of subjects experiencing a treatment emergent SAE (TESAE)
   h. the number and percentage of subjects experiencing a TESAE by toxicity grade
   i. the number and percentage of subjects experiencing a TESAE by relationship to VC-02 combination product
   j. the number and percentage of subjects experiencing a TESAE by relationship to the surgical procedures required for VC-02 administration
   k. the number and percentage of subjects experiencing a TESAE by relationship to the immunosuppressive drug regimen
ii. the number and percentage of subjects experiencing a TEAE by SOC and PT
iii. the number and percentage of subjects experiencing a TEAE by SOC, PT and toxicity grade

iv. the number and percentage of subjects experiencing a TEAE by SOC, PT and relationship to investigational product

v. the number and percentage of subjects experiencing a TEAE by SOC, PT and relationship to the surgical procedures required for VC-02 administration

vi. the number and percentage of subjects experiencing a TEAE by SOC, PT and relationship to immunosuppressive drug regimen.

vii. the number and percentage of subjects experiencing a TEAE by SOC, PT and related to investigational product

viii. the number and percentage of subjects experiencing a TEAE by SOC, PT and related to the surgical procedures required for VC-02 administration

ix. the number and percentage of subjects experiencing a TEAE by SOC, PT and related to immunosuppressive drug regimen.

x. the number and percentage of subjects experiencing a TESAE by SOC and PT

xi. the number and percentage of subjects experiencing a TESAE by SOC, PT and toxicity grade

xii. the number and percentage of subjects experiencing a TESAE by SOC, PT and relationship to investigational product

xiii. the number and percentage of subjects experiencing a TESAE by SOC, PT and relationship to the surgical procedures required for VC-02 administration

xiv. the number and percentage of subjects experiencing a TESAE by SOC, PT and relationship to immunosuppressive drug regimen.

xv. the number and percentage of subjects experiencing a TESAE by SOC, PT andrelated to investigational product

xvi. the number and percentage of subjects experiencing a TESAE by SOC, PT andrelated to the surgical procedures required for VC-02 administration

xvii. the number and percentage of subjects experiencing a TESAE by SOC, PT andrelated to immunosuppressive drug regimen.

xviii. the number and percentage of subjects experiencing a TEAE leading to study withdrawal by SOC and PT

In the overall summary of TEAEs table (i), besides tabulating the number and percentage of subjects, the total number of TEAE episodes will also be provided. If a subject has repeated episodes of a particular TEAE, all episodes will be counted in the summary table's total number of episodes.

In the remaining summary tables, the incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the SAS. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only one episode per toxicity grade, or one episode per causal relationship, will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC will be counted only once in the total of subjects experiencing TEAEs in that particular SOC. Since a subject could have more than one type of TEAE within a particular SOC, the sum of subjects experiencing different TEAEs within the SOC could appear larger than the total number of subjects experiencing TEAEs in that SOC. Similarly, a subject who has experienced a TEAE in more than one SOC will be counted only once in the total number of subjects experiencing AEs in all SOCs.

All occurrences of all AEs will be listed for each subject, grouped by cohort. The listing will contain the following information: treatment group, verbatim term, SOC, PT, toxicity grade, relationship to VC-02 combination product, relationship to the surgical procedures required for VC-02 administration, relationship to the immunosuppressive drug regimen, date and study day of onset, date and study day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE, whether it led to withdrawal and whether it is a TEAE. Listings will be sorted by cohort, treatment group (and within treatment group, the number of sentinels), subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

7.3 Clinical Laboratory Assessments

Laboratory assessments will be evaluated over time on study using descriptive statistics as described in Section 4.0. Clinical laboratory data will be summarized by study visit, cohort, and treatment group. Where appropriate, change from baseline in safety data will also be summarized in a similar manner.

7.3.1 Hematology

The hematology panel will include hemoglobin, hematocrit, red blood cell (RBC) count, platelet count, white blood cell (WBC) count, total neutrophils, eosinophils, monocytes, basophils, and lymphocytes.

7.3.2 Chemistry

Chemistry testing will include blood urea nitrogen (BUN), serum creatinine, total calcium, sodium, potassium, chloride, bicarbonate, magnesium, phosphate, uric acid, alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin (direct and indirect bilirubin reflexively measured only when total bilirubin is greater than the upper limit normal [ULN]), creatine phosphokinase, albumin, and total protein.

7.3.3 Fasting Serum Lipid Panel

The fasting serum lipid panel will include total cholesterol, high density lipoprotein cholesterol (HDL-C), calculated low density lipoprotein cholesterol (LDL-C) (Friedwald), triglycerides, very low density lipoprotein (VLDL). Non-HDL-C will be calculated as total cholesterol (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.

7.3.4 Urinalysis

Urinalysis testing will include 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.

7.3.5 Other Laboratory Tests

Other laboratory tests include serum follicular stimulating hormone (FSH) (women at screening to determine childbearing status), hemoglobin A1C (HbA1C), ultrasensitive C-peptide, urine pregnancy tests (screening and when necessary), screening serology for hepatitis B (HB) core and surface antigen/antibody (sAg/Ab), hepatitis C virus (HCV), human immunodeficiency virus (HIV) (1&2), Quantiferon, renal function evaluation via MDRD estimated glomerular filtration rate (eGFR) calculation, and thyroid stimulating hormone (TSH) (screening).

7.3.6 Immunosuppression Troughs

A listing of immunosuppression troughs will be provided.

7.3.7 Immune Panel

A listing of immune panel tests will be provided. The panel of immune function tests include:

- Humoral alloreactivity measured via human leukocyte antigen panel reactive antibody (HLA-PRA)
- Humoral autoimmunity measured via T1DM autoantibody titers of glutamate decarboxylase antibodies (GADA), insulin antibodies (IAA), islet antigen-2 antibodies (IA2A), and zinc transporter 8 (ZnT8)
- Cellular alloreactivity measured via mixed lymphocyte reaction (MLR)
- Cellular autoimmunity measured via lymphocyte stimulation test (LST)
- Cellular autoimmunity measured via Diab-Q Kit
- HLA typing of each subject (required to interpret the cellular immunity test results)

7.4 Vital Signs

Vital sign data (weight, systolic and diastolic blood pressure, heart rate, and temperature) will be summarized by presenting descriptive statistics of raw data and change from baseline values at each study visit. A listing will also be provided.

7.5 Physical Examination

A listing will be provided that includes the response to whether there are any clinically significant abnormal findings. This listing will be sorted by cohort, treatment group, and subject number.

7.6 Other Safety Analyses

7.6.1 Off-Target Growth

The number and percentage of subjects enrolled in VC02-101 Cohort 1 with off-target growth as evidenced by implanted VC-02 units via lumen ultrasound measurements, or by histological examination of explants will be summarized by cohort and treatment group.

7.6.2 Immune Sensitization

The number and percentage of subjects enrolled in VC02-101 Cohort 1 with confirmed 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 will be summarized by cohort and treatment group.

7.6.3 Implant Tolerability

The number and percentage of subjects enrolled in VC02-101 Cohort 1 experiencing implant tolerability assessments (e.g., fever, erythema, pain, tenderness, induration) for up to four hours post-implantation and at subsequent visits, will be summarized by cohort and treatment group. Implant tolerability assessments include AEs that are Possibly Related or Definitely Related to investigational product or to the surgical procedure.

8. 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 DSMB will review all accumulated data when at least a minimum of three (3) Cohort 1 subjects complete the Week 4 visit, in order to make a recommendation on enrollment of Cohort 2. In addition, a descriptive analysis may be produced when all subjects reach their Week 26 visit to support regulatory discussions. This report, if produced, will summarize key safety and efficacy endpoints for these subjects.

9. DATA SAFETY MONITORING BOARD (DSMB)

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

The approximate timing of DSMB meetings are noted below:

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

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

9.1 Internal Efficacy and Safety Review

After the last subject in Cohort 2 passes Visit 11 (Week 26), cumulative data from all Cohort 1and Cohort 2 subjects will be assembled and sent to the DSMB and Sponsor for review. If the Sponsor believes the efficacy data appear robust, and the DSMB believes the safety data are appropriate, the Sponsor may choose to proceed to an End-of-Phase 2 (EoP2) meeting with the FDA to discuss next steps.

10. SAMPLE SIZE AND POWER CALCULATIONS

At least three (3) and up to approximately fifteen (15) subjects will be enrolled in Cohort 1. Approximately 60 subjects will be enrolled in Cohort 2, for a total enrollment of up to 75 subjects in both cohorts.

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

Once the optimized device configuration and surgical implant technique is determined, a sample size of 40 subjects implanted under those conditions will provide [redacted] ince 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 provide [redacted]

11. REFERENCES

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12. APPENDICES

12.1 Appendix A: Schedule of Assessments

12.1.1 VC02-101 Cohort 1 and Cohort 2

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17 or ET	V18 Follow-Up
Assessments	**Wk -5**	**Wk -4**	**Day 1**	**Day 2**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 26**	**Wk 39**	**Wk 52**	**Wk 65**	**Wk 78**	**Wk 91**	**Wk 104**	**Wk 105**
Visit Windows		**+14d**		**+1d**	**+/- 2d**	**+/-3d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 7d**	**+/- 14d**	**+/- 14d**	**+/- 14d**	**+/- 14d**	**+/- 14d**	**+/- 7d**	**+/- 3d**
Informed Consent	X																	
Entry Criteria	X	X	X															
Med History / Prior Meds	X																	
12-lead ECG	X										X		X				X	
Physical Exam (Complete)	X										X		X				X	
Physical Exam (Abbreviated)			X		X	X		X				X			X			
Physical Exam (Targeted)				X														X
Height	X																	
Weight / Vitals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clarke Survey	X								X		X	X	X		X		X	
Immunosuppression Drug Dosing		X (adjust dosing as needed)																
Dispense / Review CGM Data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense / Review Diary Data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense / Review SMBG Supplies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Implantation Procedure			X															
Explantation Procedure				X (time-points as determined by Sponsor)													X	

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17 or ET	V18 Follow-Up
Assessments	**Wk -5**	**Wk -4**	**Day 1**	**Day 2**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 26**	**Wk 39**	**Wk 52**	**Wk 65**	**Wk 78**	**Wk 91**	**Wk 104**	**Wk 105**
Ultrasound - Safety Evaluation							X		X		X		X		X		X	
Ultrasound - Pre-Explant[a]				X (time-points TBD based on explant procedures)													X	
Video and Photos[b]			X	X (additional time-points TBD based on explant procedures)													X	
AE and Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ICD for Follow-Up Study[c]																	X	
Central Laboratory Tests or Study-Provided Testing Kits																		
Drug Screen[d]	X		X															
HBsAg, HCV, HIV	X																	
CMV IgG and IgM[g]		X											X				X	
CMV PCR		X						X			X							
EBV IgG	X																	
Hematology & Chemistry	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA1c	X		X						X		X		X		X		X	
Follicular Stimulating Hormone	X																	
Urine Pregnancy Test[e]	X		X										X				X	
Thyroid Stimulating Hormone[f]	X																	
Quantiferon TB	X																	
SOGCT C-peptide	X																	
Ultrasensitive C-peptide[h]		X					X	X	X	X	X	X	X					

	V1 [a] Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17 or ET	V18 Follow-Up
Assessments	**Wk -5**	**Wk -4**	**Day 1**	**Day 2**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 26**	**Wk 39**	**Wk 52**	**Wk 65**	**Wk 78**	**Wk 91**	**Wk 104**	**Wk 105**
2-hr MMTT/C-peptide & Glucose							X	X	X	X		X		X		X		
4-hr MMTT/C-peptide & Glucose		X									X		X		X		X	
Urinalysis	X																	
Urine Albumin/Creatinine		X									X		X		X		X	
Fasting Lipid Panel	X										X		X				X	
Immune Panel		X				X			X		X		X				X	
Reserve Blood Samples	X										X		X		X		X	
Local Laboratory Tests																		
Immunosuppression Drug Levels & Safety Panels				X (frequency as described in Section 7.11.3)														

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

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

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

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

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

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

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

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

12.1.2 VC02-102 Cohort 1

	V1 Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9 or ET	V10 FU
Assessments	**Wk -4**	**Wk -3**	**Day 1**	**Day 2**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 17**
Visit Windows				**+1d**	**+/-2d**	**+/-3d**	**+/-7d**	**+/-7d**	**+/-7d**	**+/-7d**
Informed Consent	X									
Entry Criteria	X	X	X							
Med History / Prior Meds	X									
12-lead ECG	X								X	
Physical Exam (Complete)	X								X	
Physical Exam (Abbreviated)			X		X	X		X		
Physical Exam (Targeted)				X						X
Height	X									
Weight / Vals	X	X	X	X	X	X	X	X	X	X
Immunosuppression Drug Dosing		X (adjust dosing as needed – Protocol Section **Error! Reference source not found.**)								
Dispense / Review CGM Data		X	X	X	X	X	X	X	X	
Dispense / Review Diary Data		X	X	X	X	X	X	X	X	
Dispense / Review SMBG Supplies		X	X	X	X	X	X	X	X	
Implantation Procedure			X							
Explantation Procedure				X (time-points as determined by Sponsor)					X	
Ultrasound - Safety Evaluation							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	
AE and Concomitant Medications		X	X	X	X	X	X	X	X	X
ICD for 3-Year 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	

	V1 Screen	V2 Screen	V3 Enroll	V4	V5	V6	V7	V8	V9 or ET	V10 FU
Assessments	**Wk -4**	**Wk -3**	**Day 1**	**Day 2**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 17**
HbA1c	X		X						X	
Urine Pregnancy Test[e]	X									
Follicular Stimulating Hormone[f]	X									
Thyroid Stimulating Hormone	X									
Quantiferon TB	X									
Urinalysis	X									
Urine Albumin/Creatinine		X							X	
Fasting Lipid Panel	X								X	
Immune Panel		X				X			X	
Reserve Blood Samples		X (time-points as determined by Sponsor)								
Local Laboratory Tests										
Immunosuppression Drug Levels				X (frequency as described in Protocol Section **Error! Reference source not found.**)						
Immunosuppression Safety Panels				X (frequency as described in Protocol Section **Error! Reference source not found.**)						

a. Pre-explant unit location ultrasound only required at the discretion of the Investigator. Unit location may be determined via palpation depending on anatomical location (Section **Error! Reference source not found.**).

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

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

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

e. The urine pregnancy test is administered locally using the study-provided kit.

f. FSH testing only required for women.

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