Alpha-1 Antitrypsin (AAT) Enhances Islet Autograft Survival

Clinical Study protocol

Grant #: R01DK105183

Study sponsor: NIH/NIDDK

IND Number: Waiver given by FDA

MUSC IRB Number: Pro00053906 (version 3)

Activation Date: 12/01/2015

Last Protocol Update 05/14/2020

Accrual Objective: 48

Investigational Product: Prolastin C (Alpha-1 antitrypsin, AAT)

Objectives/endpoints: To describe and compare the safety and efficacy of treatment with AAT in chronic pancreatitis patients who undergo total pancreatectomy and islet autotransplantation (TP-IAT).

Study Design: Prospective, randomized, double-blind single-center trial to assess the effects of AAT or placebo in 48 adult chronic pancreatitis patients who undergo total pancreatectomy and islet autotransplantation.

Treatment Description: Randomly selected chronic pancreatitis patients with TP-IAT will receive intravenous infusion of AAT at 60mg/kg/week or placebo weekly for 4 weeks during the peri-transplant period.

Table of Contents

1.1. PROTOCOL SYNOPOSIS

Study Sponsor	NIH/NIDDK
Investigational Product	Alpha-1 antitryspin (AAT)
Indication	Patients with chronic pancreatitis
Title of Study	**AAT Enhances Islet Autograft Survival**
Protocol Date	12/01/15
OBJECTIVES	
Primary objective: To describe and compare the safety and efficacy of treatment with AAT in chronic pancreatitis patients who undergo total pancreatectomy and islet autotransplantation (TP-IAT).	
METHODOLOGY	
Study Design	Prospective, controlled, double-blind
Treatments	Recipients will receive AAT before and post islet transplantation
Treatment Duration	Recipients will receive a total of 4 weekly infusions of AAT or placebo.
Study Drug and Formulation	Prolastin-C (Grifols)
Dose and Route of Administration	• AAT 60 mg/kg (IV) • Placebo- 0.9 % sodium chloride (IV). The first dose will be given on the day of islet transplantation before total pancreatectomy (D0), and then on days 7, 14, and 21 days of islet transplantation.
Number Planned	48
Major Inclusion Criteria	• Patients scheduled for total pancreactectomy and islet autotransplantation • Age > 18 years • Diabetes free before surgery

Exclusion Criteria	• Patients who are under immunosuppression • Patients who have had puestow or frey pancreatic surgery • Patients who have Immunoglobulin A (IgA) deficiency, known antibodies against IgA, or individuals with a history of severe immediate hypersensitivity reactions, including anaphylaxis to $Alpha_1$-proteinase inhibitor products (allergic to AAT)
Safety	• Physical examination, hematology, serum chemistry, urinalysis, vital signs, adverse event (AE) monitoring, and concomitant medications.
Efficacy	Efficacy of AAT therapy during peri-transplant period in chronic pancreatitis patients who undergo TP-IAT as assessed through islet function, onset of diabetes, glycemic control, pain relief and quality of life measurements.
ENDPOINTS	
Primary Endpoint	Area under the curve for the serum C-peptide level during the first 4 hours of an mixed meal tolerance test (MMTT), normalized by the number of islet equivalents (IEQ)/kg at day 365±14 after the transplant.
Secondary Endpoints	• Proportion of insulin-independent patients following IAT • Average daily insulin requirement. • β cell function as assessed by β-score. • Quality of life as measured by SF-12 questionnaire. Measurements will be performed at 365±14 days post-transplantation.
Exploratory Endpoints	• Measurements of primary and secondary endpoints at 75±14 day • Immediate blood mediated inflammatory response • Expression of chemokines/cytokines expression in serum • Genomic DNA analysis • RNAseq analysis of gene expression profiles in peripheral blood mononuclear cells post transplantation
STATISTICAL METHODS AND ANALYSIS	

1.2. Abbreviations:

AAT:	Alpha-1 antitrypsin
AE	Adverse Event
CP:	Chronic pancreatitis
CRF:	Case report form
CP:	Chronic pancreatitis
CFR:	Code of Federal Regulations
cGMP:	Current good manufacture practices
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Advance Event
DSMB	Data and Safety Monitoring Board
GLMM	Generalized Linear Mixed Model
HbA1c:	Glycosylated hemoglobin
HR-QOL	Health-Related Quality of Life
LOCF	Last Observation Carried Forward
IEQ:	Islet equivalent number
IBMIR:	Immediate blood mediated inflammatory response
IV:	intravenously
Kg:	Kilogram
MMTT:	Mixed meal tolerance test
mITT	Modified Intention-to-Treat
MSM	Medical Safety Monitor
PAG	Physician's Global Assessment
PBMCs:	Peripheral blood mononuclear cells
PP	Per-Protocol
QOL:	Quality of Life
SAE:	Serious Adverse Event
SOC	Standard of Care
SP	Safety Population
T1D:	Type 1 diabetes
TP-IAT	Total Pancreatectomy and Islet Autotransplantation

1.3. Study Definitions:

Insulin-independence: is defined as free of exogenous insulin for 14 or more consecutive days, with adequate glycemic control as defined by: (1) A glycated hemoglobin (HbA1c) level < 6.5%, (2) Fasting blood glucose < 126 mg/dl more than 3 times in the past week based on a minimum of once daily measurement. (3) 2-hour post-prandial blood glucose does not exceed 180mg/dl more than 4 times in the past week, (4) A laboratory fasting glucose in the non-diabetic range (< 126 mg/dl), and at least one MMTT fasting or stimulated c-peptide ≥ 0.5ng/ml

Insulin dependent: Subjects who do not meet the criteria for insulin independent.

Adverse events (AE): According to the International Conference on Harmonization (ICH) Guidelines (Federal Register.19995;60 (40):11285), an AE is defined as follows: An AE is any untoward medical occurrence in a subject administered an investigational drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product whether or not related to the investigational product. An AE is any sign, symptom, or diagnosis that appears or changes in intensity during the course of the study. An AE may be an intercurrent illness or an injury that impairs the well-being of the subject.

Severe hypoglycemia: Severe hypoglycemia is an event with one of the following symptoms: memory loss; confusion; uncontrollable behavior; irrational behavior; unusual difficulty in awakening; suspected seizure; seizure; loss of consciousness; or visual symptoms, in which the subject was unable to treat him/herself and which was associated with either a blood glucose level < 54 mg/dL or prompt recovery after oral carbohydrate, IV glucose, or glucagon administration.

2. BACKGROUND AND RATIONALE:

2.1. BACKGROUND:

2.1.1. Total Pancreatectomy and islet autotransplantation (TP-IAT):

Chronic pancreatitis (CP) is a disease in which long-standing inflammation of the pancreas alters the normal structure and function (1). Approximately 15,000 Americans are diagnosed with CP each year. Recurrent bouts of pancreatitis result in inflammation, scarring, and blockage of the pancreatic ducts. These effects produce chronic pain that is difficult to control with medications. TP-IAT is currently being performed in around 20 centers worldwide and can effectively increase patients' quality of life and ameliorate post-operative diabetes in well-selected CP patients. A major hurdle in this procedure is that less than 30% of patients return to an insulin-independent state after TP-IAT, compared to a >85% diabetes-free rate before surgery. Compromised islet function is caused by pre-operative loss of beta cell mass from long-term inflammation within the diseased pancreas, but also by dramatic stress-induced islet cell death during harvest and post transplantation. Currently, no interventional protocols are in place to improve islet autograft survival and function in TP-IAT patients. Our long-term clinical research goal is to apply effective therapies that can facilitate islet cell survival and function to benefit patient care. These therapies are not only urgently needed for the prevention of post-surgical diabetes in CP patients, but can potentially serve as a powerful platform on which to investigate strategies for allogeneic islet cell transplantation for patients with T1D.

2.1.2. Alpha-1 antitrypsin (AAT)

AAT is a serine protease inhibitor that belongs to the serpin family. It has a high concentration in serum, and is available for clinical use as an affinity-purified human product (2). AAT inhibits various enzymes including neutrophil elastase, cathepsin G, proteinase-3, thrombin, trypsin, and chymotrypsin (3). Patients with a genetic deficiency in AAT exhibit 15-60% lower circulating AAT levels than normal and are prone to develop pulmonary emphysema (4). Besides inhibition of neutrophil elastase, AAT exerts anti-inflammatory effects via suppressing cytokine production, complement activation, and immune cell infiltration. AAT also functions as an anti-apoptotic factor for endothelial cells and vascular smooth muscle cells (5,6). AAT induces vascular endothelial growth factor (VEGF) expression and release, protects VEGF from proteolytic cleavage by elastase, promotes viability of endothelial cells, and enhances migration of myocytes. Recent studies indicated that AAT had profound beneficial effects in the treatment of diabetes. AAT protects β cells from apoptosis induced by pro-inflammatory cytokines and streptozotocin (7). A single injection of AAT to NOD mice reduced the intensity of insulitis, increased β cell mass, promoted β cell regeneration, and prevented the onset of diabetes via modulating T regulatory cells (8,9). AAT has been shown to protect islets from graft failure and immune rejection in mouse transplantation models with readily vascularized islet grafts (10,11). Adding AAT into ductal injection solution and collagenase solution improved porcine islet isolation by inhibiting trypsin activity during pancreas digestion (12). AAT monotherapy

elevates VEGF expression levels in islet allograft and prolongs islet allograft survival in mice via enhancement of intraislet VEGF expression and promotion of islet revascularization (11).

A recent study published by Koulmanda and colleagues demonstrated that AAT treatment improved survival of islets after partial pancreatectomy and intrahepatic autologous islet transplantation in non-human primates (13). Thus, the beneficial effects of AAT in the islet transplantation setting may be mediated by its anti-apoptotic and anti-inflammatory properties and promotion of islet revascularization.

2.1.3. Clinical trials use of AAT for diseases:

Several clinical trials have been performed evaluating the effects of AAT in new onset diabetes. One trial entitled "A research trial of Aralast in new onset diabetes (RETAIN)", gave patients with new onset T1D AAT (Aralast NP) at 45mg/kg by intravenous infusion once a week for 6 weeks, and then a 3 week wash out, followed by a high dose of AAT at 90mg/kg for the next 6 weeks, with a total of 12 infusions. Data from this trial has yet to be published.

In another phase 1 open label trial in 12 new onset T1D patients treated with 80mg/kg of AAT weekly for 8 weeks, AAT led to increased, unchanged, or moderately reduced levels of C-peptide responses compared with baseline in 5 patients. No control group is available for comparison. In addition, mechanistic analyses revealed reduced levels of toll-like receptor-induced interlukin-1β expression in monocytes and dendritic cells at 12 months post AAT treatment (14).
Most importantly, AAT has been used for the treatment of emphysema for more than 25 years with a remarkable record of safety (15), therefore it is an ideal candidate to be used in the islet transplantation setting to improve the efficacy of clinical islet transplantation.

2.2. RATIONALE:

2.2.1. Rationale for Selection of patient population:

Although the beneficial effects of AAT have been demonstrated in rodents and non-human primate islet transplantation models, its potential therapeutic effect has not been evaluated in patients with islet transplantation. We designed this randomized, double-blind, placebo control study to assess the safety and efficacy of 60 mg/kg of weekly IV injection of AAT in subjects with autologous islet transplantation. Unlike patients with type 1 diabetes, there is no recurrence of autoimmunity and immune rejection response in patients receiving autologous islets. Therefore, it is a suitable disease model to evaluate the protective effect of AAT to transplanted islets.

2.2.2. Rationale for the Selection of Dosing Regimen

AAT (Prolastin-C, Grifols) used in the current trial has been given a waiver for IND by the FDA.

Prolastin-C is indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of AAT. The dosing regimen of Prolastin-C chosen for this study, 60 mg/kg given intravenously once per week, is the standard FDA-approved dosing regimen for emphysema, and is identical to other plasma-derived AAT products in the same class. At this dosage, Prolastin-C has been demonstrated to be safe and well tolerated in subjects with congenital AAT-deficiency, and was shown to increase and maintain circulating trough antigenic and functional AAT levels to 14.7 μM (median; range: 11.6-18.5 μM) and 11.9 μM (median; range: 8.2-16.9 μM), respectively (see Prolastin-c package insert).

2.2.3. Rationale for the Selection of Route of Administration and Infusion Rate

The route of administration (intravenous infusion), as well as the infusion rate (0.08ml/kg/min), selected for this study are in accordance with the FDA-approved package insert.

2.3. KNOWN AND POTENTIAL RISKS AND BENEFITS TO HUMAN PARTICIPANTS

2.3.1. General risks

Transplantation of islets is associated with several potential risks. These are intrinsic to the procedure and may result from the intrahepatic islet infusion as well as testing involved in the care and evaluation of transplanted subjects. All patients receiving TP-IAT are at risk of complication regardless of study participation.

2.3.2. Risks of use of Investigation product: Prolastin-C

Because clinical studies for Prolastin-C are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice. According to the Prolastin-C package insert, the most serious adverse reaction observed during clinical studies with Prolastin-C was an abdominal and extremity rash in one subject. The rash resolved subsequent to outpatient treatment with antihistamines and steroids. Two instances of a less severe, pruritic abdominal rash were observed upon re-challenge despite continued antihistamine and steroid treatment, which led to withdrawal of the subject from the trial.

The most common drug-related adverse reactions observed at a rate of > 1% in subjects receiving Prolastin-C were chills, malaise, headache, rash, hot flush and pruritus. Adverse reactions considered drug related by the investigators occurring in 1.6% of subjects (one subject each) treated with Prolastin-C were malaise, headache, rash, hot flush, and pruritus. Drug related chills occurred in 3.2% (2 subjects) of Prolastin-C subjects.

Products made from human plasma may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. In each of 2 randomized, double-blind studies in which the predecessor product, PROLASTIN® (Alpha1-Proteinase Inhibitor [Human]), was compared to other AAT products, there was a single case of parvovirus

B19 seroconversion in the Prolastin-C arms of each trial. In each case, it could not be determined whether parvovirus had been acquired from Prolastin-C or from the community. However, during clinical studies with Prolastin-C, there were no reported treatment emergent cases of hepatitis B, hepatitis C, HIV or parvovirus B19 viral infections. Furthermore, the Prolastin-C process incorporates additional plasma safety and virus reduction measures that minimize the residual risk of virus transmission. Risk for placebo: patient may not be receiving a therapy as good as the alternative arm of the study. There is no other risk to placebo infusion at the dose provided.

2.3.3 Risks of blood sampling

In addition to the routine blood sampling, participation in the study will require an amount of blood higher than routine sampling at some time points, so that biomarkers of inflammation, chemokine/cytokines, and RNA expression can be measured. The risks of drawing blood include temporary discomfort from the needle stick, bruising and infection. Fainting could occur.

2.3.4. Other study related procedures

All other procedures including islet transplantation, c-peptide, and glucose testing are part of standard patient care and would be performed regardless of study participation.

2.4. POTENTIAL BENEFIT

2.4.1. Benefits to TP-IAT patients

There is no proven benefit to participants by entering this clinical trial. It is hoped that AAT treatment participants will have improved graft survival; however, this remains to be shown.

2.4.2. Benefits to society

This study may identify a useful medication that will benefit patients with islet transplantation.

3. OVERALL STUDY DESIGN AND PLAN DESCRIPTION:

3.1. STUDY DESIGN:

Experimental design: We propose to enroll a total of 48 CP patients who are scheduled for TP-IAT. This will be a 2:1 randomized, double blind, controlled study in which 32 patients receive islet cell transplantation together with intravenous AAT 60 mg/kg/week for 4 weeks, and 16 patients receive islets with intravenous 0.9% saline control in equivalent volume.

CP patients planning TP-IAT will receive an IRB approved consent form that describes the research study. Following signed consent, they will be enrolled and receive a baseline study visit. On the day of TP-IAT, an intravenous injection of AAT at the FDA approved dose of 60mg/kg or 0.9% normal saline will be infused before surgery. The autologous islet transplantation procedures will remain as routinely performed at MUSC. On the day of transplantation, the pancreas will be harvested and transferred to the Center for Cellular Therapy (CCT). Islets will be isolated and transplanted back to the patient via portal vein infusion. AAT or placebo will be given on day 0, 7, 14 and 21 days of islet transplantation.

3.2. STUDY TIME TABLE

Planned patients are expected to be recruited in a 36-month period. A follow-up of 12 months is planned for each patient. The overall timelines are as below:

- Projected starting data (first-patient-in): June 1, 2016
- Projected completion of patient accrual (last-patient-in): May 31, 2019
- Projected study end date: May 31, 2020

3.3. END OF STUDY

For this trial, end of the study is defined as the date of the last visit of the last patient.

3.4. STUDY OBJECTIVE

The objective of this clinical trial is to describe and compare the safety and efficacy of treatment with AAT in chronic pancreatitis patients who undergo TP-IAT.

3.5. STUDY ENDPOINTS:

3.5.1. Primary endpoint:

The primary endpoint will be Area under the curve for the serum C-peptide level during the first 4 hours of an mixed meal tolerance test (MMTT), normalized by the number of islet equivalents (IEQ)/kg at day 365±14 after islet transplant.

3.5.2. Secondary endpoints (measurements will done at 365±14 days post-transplantation):

- Proportion of insulin-independent patients following IAT.
- Average daily insulin requirement.
- β cell function as assessed by β-score.

3.5.3. Exploratory endpoints

- Measurements of primary and secondary endpoints at day 75±14.
- Time course of instant blood mediated inflammatory reaction as measured by thrombin-anti-thrombin (TAT), C5a and c-peptide levels before, in the middle and after initiation of islet infusion, and 3h post islet infusion.
- Time course of inflammatory chemokines/cytokines as assessed by serum level of CXCL8, CCL2 (MCP-1), CCL3, CCL4, CXCL10 (IP-10), CXCL9 (MIG), IL-6, IL-10, INF-γ, TNF-α, and IL-1β [pre-infusion, and 24, 72 and 168hrs, and day 14, and 21 after the end of islet infusion].
- Basal to 240 min time course of glucose, and C-peptide derived from the MMTT (day 75±14 to day 365±14).
- The proportion of patients with an HbA1c ≤6.5% (day 365±14 days post-transplant only)
- Cumulative number of severe hypoglycemia events.
- The proportion of patients with an HbA1c ≤6.5% at day 365±14 AND are free of severe hypoglycemic events from day 75±14 to day 365±14 inclusive.
- Daily oral Morphine Equivalents on day prior to visit (day 75±14 to day 365±14).
- Proportion of patients remaining on narcotics (day 75±14 to day 365±14).
- RNA expression profile in peripheral blood mononuclear cells (PBMCs) at 168 h post transplantation. RNA analysis will be done in at least 10 patients to guarantee post-treatment sampling in at least 3-4 patients randomized to AAT and 3-4 to control.
- SF-12 Quality of Life score

3.5.4. Safety endpoints:

- Incidence and severity of Adverse Events and Serious Adverse Events
- Standard laboratory tests including hematology (hematocrit, hemoglobin, red blood cells, platelets, white blood cells, differential white blood cell count), clinical chemistry (sodium, potassium, serum creatinine, blood urea nitrogen, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and coagulation (International Normalized Ratio (INR), partial thromboplastin time (PTT)), at pre-transplant hospital admission and post-transplant hospital

discharge].

- Vital signs, i.e. blood pressure (BP) and heart rate (HR) at pre-transplant hospital admission and post-transplant hospital discharge. ALT/AST, INR/PTT
- Weight loss from pre-transplant value [time frame: day 75+14 and 365±14 after the transplant]
- Serum level of albumin and pre-albumin (absolute and change from pre-transplant value) [time frame: day 75±14 and 365±14 after the transplant].
- Proportion of patients falling into one of the following levels of steatorrhea severity [time frame: day 75±14 and 365±14 after the transplant];
  1. No steatorrhea;
  2. Steatorrhea few times per week;
  3. Steatorrhea daily;
  4. Stool incontinence.
- Proportion of patients falling into one of the following malnutrition risk levels (poor prognosis, significant risk, increased risk, normal) according to pre-albumin level [time frame: day 75±14 and 365±14 after the transplant].
- Cumulative number of episodes of documented hypoglycemia (documented symptomatic; asymptomatic) [time frame: from day 75±14 to day 365±14 after the transplant].
- Cumulative number of diabetic ketoacidosis-related events [time frame: from day 75±14 to day 365±14 after the transplant].

4. STUDY POPULATION

CP patients scheduled for TP-IAT will be enrolled in this study. Our recruitment goal is to reach a total of 48 patients, each randomized to receive either standard of care (SOC) plus placebo or SOC with AAT after consent.

4.1. Inclusion criteria

- Patients scheduled for total pancreactectomy and islet autotransplantation
- Age ≥ 18 years
- Diabetes free before surgery

4.2. Exclusion criteria

- Patients who are under immunosuppression (eg. more than 5 mg prednisone use of another immunosupressive drug including but not limited to methotrexate, cyclosporine, tacrolimus, azathoprine, sirolimus, or rituxan).
- Patients who have had puestow or frey pancreatic surgery
- Patients who have Immunoglobulin A (IgA) deficiency, known antibodies against IgA, or individuals with a history of severe immediate hypersensitivity reactions, including anaphylaxis to $Alpha_1$-proteinase inhibitor products (allergic to AAT)

4.3. Assignment of patient number

Once patient is determined eligible for the study, and randomized into a group, they will be assigned a unique number for the study. This patient is then evaluable under intention to treat analysis as defined in the statistical plan.

5. INVESTIGATIONAL PRODUCT

5.1. Investigational product:

5.1.1. Prolastin-C (Grifols) is human alpha-1 proteinase inhibitor (AAT) that is indicated for chronic augmentation and maintenance therapy in adults with emphysema due to deficiency of alpha1-proteinase inhibitor. Prolastin-C is approved in the US, Canada, Columbia, and Argentina for 60 mg/kg weekly IV administration for augmentation therapy in patients with severe AATD and clinically evident emphysema. It is a sterile, stable, lyophilized preparation of purified human protein inhibitor. Prolastin-C is prepared from pooled human plasma from healthy donors by modification and refinements of the Cohn cold ethanol plasma fractionation technique followed by a purification process. Prolastin-C contains small amounts of other plasma proteins, which may include IgA, haptoglobin, alpha1-acid glycoprotein, lipoprotein A-1, and albumin. Reconstituted Prolastin-C contains no preservatives, has a pH of 6.6 to 7.4, and is to be administered by the IV route.

5.1.2 Placebo

Placebo used in this study will be 0.9% Sodium Chloride for Injection, USP.

5.2. FORMULATION, DOSING, ADMINISTRATION AND EMERGENCY PRECAUTIONS

Prolastin-C is commercially available, and packed as a lyophilized powder and is ready to use after reconstitution with dilute (sterile water) that comes with the drug. Each pack contains 1000mg of AAT, and 20ml of dilutant. Both Prolastin-C and the dilutant should be stored at temperature not to exceed 25 (77 ° F). Reconstituted product from several vials may be pooled into an empty, sterile IV solution container by using aseptic technique. All the materials will have trial specific labels. The reconstitution should be used within 3 hours. The dosing will be administered at a rate of approximately 0.08ml/kg/min. The 60mg/kg dose takes approximately 15-30 minutes to infuse. If assigned to the placebo group, saline will be infused at the same volume and speed.

Each patient will receive 60mg/kg body weight if assigned in the AAT group. The first dose will be calculated based on the recipient's body weight during admission for transplant. The subsequent doses will be calculated based on the body weight recorded at study entry. The final dose for infusion will be rounded to the nearest whole vial dose, but must be within 10% of calculated dose.

The first infusion of the Investigational Product will start on the day of islet transplantation. Patient will receive 4 weekly doses of AAT or saline 7 ± 3 days apart.

The Investigational Product will be dispensed only by a qualified individual. Vital signs will be recorded within 30 minutes before the infusion, during infusion and 15 minutes after infusion. With each infusion, medical personnel will be available to treat subjects who experience difficulties. Emergency treatment such as 0.3ml to 0.5ml aqueous epinephrine (1:1000 dilution) subcutaneously and other resuscitative measure including oxygen, IV fluids, antihistamines, corticosteroids, vasopressors, and airway management, will be available in the infusion suite.

5.3. DRUG ACCOUNTABILITY

Under Title 21 of the Code of Federal Regulation (21CFR{312.62 Investigator recordkeeping and record retention.), an investigator is required to maintain adequate records of the drug preparation and disposition, and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation.

Records for receipt, storage, use and disposition will be maintained by the unblinded study coordinator. A drug dispersement log including the identification of each subject, date and quantity of drug used will be kept current for each subject. Any drug accidentally or deliberately destroyed will be recorded as well.

5.4. CRITERIA FOR SCHEDULE ADJUSTMENT, DOSE–MODIFICATION, DISCONTINUATION OF INVESTIGATIONAL DRUG.

5.4.1. No schedule adjustment and/or dose modification is foreseen, except for discontinuation of drug as detailed below:

5.4.2. Criteria for discontinuation of Investigational Product

Any subject may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the appropriate CRF. Patients who discontinue the treatment with the investigational drug will not be withdraw from the study by default, but will complete observations as per the protocol, unless otherwise they withdraw their consent.

Discontinuation (ie, complete withdrawal from study participation) may be due to dropout (ie, active discontinuation by subject) or loss to follow-up (ie, discontinuation by subject without notice or action), or death. Additionally, the investigator and sponsor have the discretion to discontinue any subject from the study if, in their judgment, continued participation would pose an unacceptable risk for the subject. Subjects meeting the definition for intent-to-treat who are prematurely terminated from study treatment will not be replaced.

5.5. STUDY STOPPING RULES

Study enrollment will be suspended pending review of all pertinent data by the institutional review board (IRB), and the Data Safety Monitoring Board (DSMB), if any of the following occurs:

- Any unexpected fatal or life-threatening AE possibly related to the use of the Investigational drug.
- Any event(s) the protocol chair determines will require full DSMB review.
- The DSMB recommends termination of protocol enrollment based on review of the data and evidence that such action is necessary.

6. STUDY PROCEDURE AND ASSESSMENTS:

6.1. HOSPITAL STAY

6.1.1. Patient recruitment, blinding and randomization

Subjects will be recruited from the clinical offices of Drs. David B Adams and Katherine A Morgan during their routine preoperative evaluation for pancreas resection and islet transplantation. During their preoperative evaluation, the purpose of the study and the associated consent form will be explained in detail and the participant will be given time to ask questions. If the subject wishes to participate, the proper consent and HIPAA forms will be signed and dated. The consent form may be signed in person in a clinic or via telehealth using an eConsent/doxy.me. On the doxy.me platform the study participant has the ability to download a copy of the signed consent for their record. They will be informed of this and encouraged to download their copy by the study team member who is obtaining consent. The virtual visit video chat feature of this platform allows for questions from the patient to be answered in real time by the study team. The study team member obtaining consent will also have the ability to review the HIPAA authorization form with the patient and obtain a signature through the doxy.me platform. A copy of the signed consent form will accompany the patient to the operating room for documentation of participation in the study.

Consented patients will be screened based on inclusion and exclusion criteria. If patient meets the criteria, they will be randomized to either AAT or control group by block randomization. The PI (Wang) and the clinical PIs (Morgan, Adams, Strange, Luttrell) of this study will be blinded for the assignment of the study treatment. The Investigational Pharmacy at MUSC will prepare drug infusions using aseptic technique under a sterile hood. In the clinic, a trained RN will infuse the drug and monitor for side effects of AAT, These individuals will not be blinded.

Diabetes care will be managed by the Endocrinology team at MUSC led by Dr. Louis Luttrell, co-investigator of our trial. The diabetes care is standardized while in the hospital with insulin drip for all patients post-operatively. The drip is then weaned over the first few days with care individualized by the hospital diabetes management team. The discharge plan is then individualized in accordance with ADA standards.

The required lab tests for the study include an IgA level and the MMTT at time 75 and 365 days. There are no imaging screening tests required for this study. It is noted that many of the safety laboratories will be the same laboratory assesssments as are used for the usual surgical care.

One basal serum sample will be collected prior the first infusion of study drug (AAT or normal saline) and be stored for pre-transplant chemokines/cytokines. The basal sample will be obtained before surgery.

6.1.2 Infusion of the Investigational Product

Infusion of AAT will start on the day of islet transplantation before anesthesia and pancreatectomy, which is approximately 6-8 hours before islet infusion. The clinical PIs, Drs. Morgan and Strange, will identify the time to start the study drug infusion. Starting and ending time of drug administration, amount of drug infused, and infusion rate will be recorded for each subject. On Average, TP-IAT patients stay in the hospital for 7-28 days after islet transplantation. If they stay till 21 days post transplantation, they can have all four AAT injections in the hospital. If they are discharged earlier, patients will be requested to return to MUSC for additional drug infusion(s). A nurse will administer the AAT or placebo infusion to the patient while in the hospital. A nurse in the GI surgery clinic or SCTR outpatient clinic will administer AAT or placebo to patients discharged but returning for one of the weekly visits. The nurses infusing these drugs will be trained on the day of administration concerning the few known side effects of AAT and rate of infusion.

6.2. DRUG ADMINISTRATION POST HOSPITAL STAY

In the case when patient is discharged before completion of 4 doses of AAT, they will be asked to return to MUSC at the required times to get the investigational drug administered. Starting and ending time of drug administration and the infusion rate will be recorded for each drug administration. Serum AAT level will be measured before and 30 mins after the first drug administration.

6.3. POST-OPERATIVE ASSESSMENTS

All routine measurements for TP-IAT patients will be measured according to current protocols for this patient population. SF-12 Quality of life and reduction in narcotic dose of morphine or equivalent will be obtained fromthe Islet Longitudinal Outcome Database (ILOD) which has granted this project authorization to use their information. . The following will be assessed during hospital stay and each time or when patients return for drug injection:

6.3.1. Instant blood mediated inflammatory reaction (IBMIR): 3ml of blood will be collected before AAT injection, before, in the middle, and after initiation of islet infusion and 3h post islet infusion. Serum will be collected and stored in -70 ° C for analysis of thrombin-anti-thrombin complex (TAT), C5a, and c-peptide level.

6.3.2. Chemokines/cytokines: A blood sample will be obtained at 0, 24, 72, and 168 h (before AAT injection), and day 14 (before AAT injection), and 21 (before AAT injection) post transplantation to measure chemokine and cytokine expression in the serum using the Lumix machine. Each time 5 ml of blood will be collected and centrifuged; aliquots of serum will be stored in in -70 ° C for further analysis.

6.3.3. DNA testing: A 10 ml whole blood sample will be collected during screening, and stored in -70 ° C for isolation of genomic DNA for further analysis. This future analysis may be conducted by the PI or by other researchers who obtain IRB approval for their research. This research may involve genetic studies. The specimens will be labeled with a code that only study personnel can link back to the patient. Researchers outside of this study will not be given a link between the code number and patient's name or any other identifying information. We expect to store the specimens long-term for future studies on disease condition. Participant will not be contacted for additional consent. The investigators will not tell patient what they find out about the patient, nor will contact the patient if a test becomes available to diagnose a condition that a patient might have or later develop. Results will not be placed in the individual participant's medical record.
There is a risk of potential loss of patient's privacy or confidentiality. Information about race, ethnicity, sex, medical history, and so forth might be available to investigators studying the specimen. Such information might be important for research or public health. It is possible that this information (including genetic information) might come to be associated with patient's racial or ethnic group. The specimens obtained from patients in this research may help in the development of a future commercial product. There are no plans to provide financial compensation to patient should this occur. Whether patient will agree to have their blood stored will not impact their participation in the study.

6.3.4. RNA and other analyses: PBMCs (10ml blood) and plasma (15ml of blood) will be collected at 168 h post transplantation and stored in -70 °C for RNA expression, proteonomics, metabolics and small RNA analysis.

6.3.5. The total amount of blood drawn for research purposes will be 145 ml (10 tablespoons) over the course of the study.

6.3.6. Mixed meal tolerance test (MMTT)
MMTT tests will be performed at 75±14 and 365±14 days post-surgery. During the MMTT, patients will be asked to drink a special drink called 'BOOST', which will be given at a dose of 6 mL per kilogram body weight and contains a mixture of protein, fat and carbohydrates. Patient's blood will be draw at 0, 15, 30, 60, 90, 120, 180 and 240 min after drinking the boost. In each time point, 4ml of blood will be collected, 2ml for measuring blood glucose, and 2ml to measure c-peptide levels. Samples will be sent to the blood lab for analysis.

6.3.7. Safety laboratory tests:
Laboratory tests will be performed before hospital discharge. These are standard of care tests done in all TP-IAT patients.

6.3.6.Vital signs: Blood pressure and heart rate will be measured before hospital discharge.

6.4. FOLLOW-UP VISITS:

Autologous islet transplant recipients will be followed up life-long in our center. For this study specifically, patients will be followed up till 12 months post-transplantation. They will have to attend 2 follow-up visits scheduled on day 75±14 and 365±14 days after the transplant, this can be combined with their routine returning visits.

6.4.1. Mixed meal tolerance test (MMTT)

MMTT tests will be performed at 75±14 and 365±14 days post-surgery.

7. SATETY MONITORING

7.1. DEFINITIONS:

7.1.1. Definition of Adverse Events (AEs)

According to the International Conference on Harmonization (ICH) Guidelines (Federal Register.19995;60(40):11285), an AE is defined as follows: An AE is any untoward medical occurrence in a subject administered an investigational drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product whether or not related to the investigational product. An AE is any sign, symptom, or diagnosis that appears or changes in intensity during the course of the study. An AE may be an intercurrent illness or an injury that impairs the well-being of the subject.

Unchanged chronic conditions or those related to the underlying disease or medical conditions that are consistent with natural disease progression are not AEs and should not be recorded on the AE pages of the case report form. These medical conditions should be adequately documented on the appropriate page of the form (medical history or physical examination). However, medical conditions present on the first day of treatment that worsen in intensity or frequency during the treatment or post-treatment periods should be reported and recorded as AEs. The Investigator will actively solicit this information from the subject and assess the event in terms of severity and relationship to the study treatment regimen.

7.1.2. Definition of Serious Adverse Events (SAEs)

An AE occurring with any study treatment regimen should be classified as “Serious” if it meets one of the following criteria:

- It results in death (i.e., the AE caused or led to death).
- It is life threatening (i.e., the AE placed the subject at immediate risk of death). This classification does not apply to an AE that hypothetically might cause death if it is more severe.

- It requires or prolongs inpatient hospitalization (i.e., the AE requires at least a 24 hour inpatient hospitalization or prolongs a hospitalization beyond the expected length of stay). Hospitalizations for elective medical or surgical procedures, scheduled treatments, or routine checkups are not SAEs by this criterion.
- It is disabling or incapacitating (i.e., the AE results in a substantial disruption of the subject's ability to carry out normal life functions).
- It is a congenital anomaly or birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed the molecule or study treatment regimen before conception or during pregnancy).
- It does meet any of the above criteria, but could jeopardize the subject and might require medical or surgical intervention to prevent one of the outcomes listed above.

7.1.3. Evaluation of Adverse Events

Serious AEs should be graded with respect to severity on the following 3 point scale and reported, in detail, on the appropriate CRF page:

Grade 1: Mild AE. Discomfort noticed, but no disruption of normal daily activities; event usually requires no intervention.
Grade 2: Moderate AE: Discomfort sufficient to reduce or affect normal daily activities; even may require intervention.
Grade 3: Severe and undesirable AE: Incapacitating, with inability to perform normal daily activities; event usually requires treatment or other intervention. Subject may not be able to continue in the study.
Grade 4: Life-threating or disabling AE
Grade 5: Death

The Investigator should evaluate the relationship of each SAE to the study treatment regimen, using the following criteria:

- **Unrelated:** Another cause of the SAE is more plausible; a clinically plausible temporal sequence is inconsistent with the onset of the AE and administration of the study treatment regimen; or a causal relationship is considered biologically impossible.
- **Possibly related:** There is a clinically plausible time sequence between onset of the SAE and administration of the study treatment regimen, but the SAE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. "Possibly Related" should be used when the study treatment regimen is one of several biologically plausible SAE causes.
- **Definitely Related:** The SAE is clearly related to use of the study treatment regimen.

7.2. Procedures for Recording and Reporting Adverse Events

Fatal or life-threatening events thought to be caused by Study Drug will be reported to the Chair

of the DSMB and the MUSC IRB. There are no events that are expected to occur as a result of AAT or placebo infusion.

Serious AEs require expedited reporting to the DSMB Chair or designee, regardless of the relationship of the event to the study treatment regimen. Refer to the previous section for the definition of a serious adverse event.

Investigators will report all SAEs to the DSMB Chair or designee within the timelines of NIDDK policy after observation or learning of the event. For initial SAE reports, the Investigator should record all case details that can be garnered on the SAE form and the AE CRF page. Relevant follow-up information is to be submitted to the Sponsor or its designee as soon as it becomes available.
Adverse Events will be reported to the IRB and the NIDDK program officer. The DSMB will review all safety data and all adverse events that occur (see section 7.3). The MUSC Internal Review Board will also monitor this study.

7.2.2. Special Reporting Situations

- **Death:** Death is an outcome of an event. The event that resulted in death should be recorded and reported on the SAE form and the AE CRF page.
- **Hospitalization for Surgical or Diagnostic Procedures:** The illness leading to the surgical or diagnostic procedure is to be recorded as the SAE, not the procedure itself. The procedure is to be captured in the case narrative as part of the action taken in response to the illness.

7.3. Data Safety Monitoring Board (DSMB):

DSMC recommended by the NIDDK will meet to approve the protocol and the statistical plan before patient recruitment. The DSMC meeting frequency will be determined by the NIDDK. We suggest that the committee meet after the 5th patient has been treated, so that safety issues can be discussed. We will send quarterly SAE/AE reports to the committee according to the safety procedures described above. Safety procedures have been in place for our current islet autotransplantation procedure at MUSC. Any Suspected Unexpected Serious Adverse Reaction will lead to interruption of study recruitment until the DSMC has reviewed and approved recommencing. An update of the progress of the study including an efficacy and safety report be submitted to the DSMB every 6 months during the conduction of the study and a report at the end of it.

8.STATISTICAL ANALYSIS:

8.1. STATISTICAL ANALYSIS PLAN AND STATISTICAL REPORTS

The following section provides the details of statistical analyses planned, including safety and primary and secondary efficacy endpoints. In addition, it discusses the statistical issues relevant to these analyses (e.g., sample data to be used, missing data).

The Statistical and Data Management Center (SDMC) generates a closed statistical report to be distributed only to the DSMB. The timing of the report is determined in consultation with the DSMB. Reports will be sent from the SDMC to the NIDDK two weeks in advance of the scheduled meeting.

Each report provides cumulative summary statistics on enrollment; subject status in the study; baseline characteristics; protocol violations; safety data, including AEs and SAEs, severity, expectedness and relatedness to the study treatment; and data management/quality information (e.g., timeliness and completeness of data entry; number of data clarification requests generated and resolved). The statistics are provided for the overall study in the open report. For the closed report only, the statistics are also provided by partially blinded treatment groups (A vs B). Due to the unequal allocation used in this study, partially blinded reports will not include the counts.

8.2. ANALYSIS POPULATION:

8.2.1. MODIFIED INTENT-TO-TREAT POPULATION

The modified intent-to-treat (mITT) population includes all randomized subjects who meet study eligibility criteria and have received at least one injection (of AAT or placebo). The primary efficacy measures will be analyzed with the mITT population.

8.2.2. PER-PROTOCOL POPULATION

The per-protocol (PP) population includes all randomized subjects who meet the study eligibility criteria, completed the assigned treatment infusions, and have the primary efficacy endpoint assessed.

8.2.3 SAFETY POPULATION

The safety population (SP) includes all subjects for whom consent is obtained and surgery is performed.

8.3. SAMPLE SIZE JUSTIFICATION

We recognize that the number of participants is small given the heterogeneity of chronic pancreatitis but believe the numbers are appropriate for a proof-of-concept translational study. The goal of this aim would be to test whether IAT + AAT is feasible in this patient population and to obtain preliminary assessments of its success. Having n=32 subjects treated with AAT

(and n=16 placebo controls) would allow us to make relatively precise estimates of feasibility measures and means of the study outcomes, with 95% confidence intervals that would extend approximately 0.3 standard deviation units in either direction. While recognizing that the standard deviation will be slightly higher in the control population, we recognize that all hypothesis testing will be considered exploratory, enabling 80% power to detect moderately large differences (effect sizes of 0.9 standard deviation units) between the AAT and treated control groups with respect to the study outcomes, including the 4 hour C-peptide level AUC obtained at 12 months, assuming up to a 10% loss to follow-up over the 12 months. Having these numbers of subjects would also allow us to make preliminary comparisons between outcomes in the IAT + AAT group and outcomes observed in a group of 150 historical controls, each of whom received a total pancreatectomy with IAT at MUSC from 2009-2015. Most importantly, the data (e.g. means, standard deviations, and effect size estimates) from 32 subjects receiving AAT treatment, 16 control subjects receiving islets alone, and 150 historical controls will be vital for use in designing a larger more definitive randomized controlled trial in the future. Using 2:1 randomization will help provide more precise estimates of outcomes in the IAT + ATT group and may also help with study recruitment, as subjects may tend to be more willing to consent if they have a stronger probability of receiving the active experimental treatment.

8.4. RANDOMIZATION

A randomization system will be developed by the biostatistician. The objective of randomization is to prevent possible selection bias by providing random treatment assignment to each subject; and to maintain treatment balance with respect to relevant prognostic variables.

Each cohort will start from a permuted block randomization with a block size of 6, including 4 assignments to the AAT arm and 2 assignments to the placebo arm. This initial block of 6 patients will provide information for early safety assessment of AAT.

Following the initial block, additional subjects will continued to be randomized between AAT and placebo in a 2:1 fashion, using random block sizes of 3 and 6.

8.5. BLINDING

The study will be conducted in a double blind manner. Identical study treatment infusion packages will be prepared by our clinical trial coordinator. Study subjects, treating investigators, and efficacy endpoint assessors will be blinded to treatment assignments.

The clinical trial coordinator will produce identical sealed envelopes that contain identification of treatment codes. Prior to initiation of the trial, these envelopes will be stored in a locked file cabinet at the coordinator's office in its limited access central file room.

The DSMB will be partially unblinded for the closed reports (data reported by treatment groups "A" and "B" only). However, if it so wishes, it may be completely unblinded at any time during the trial. If the DSMB wishes to be unblinded on a particular subject only, the NIDDK Liaison to the DSMB should email the request to the unblinded biostatistician.

8.6. MISSING DATA

All efforts will be put forth to ensure near complete follow-up, in particular with the assessment of the primary outcome at 12 months and occurrence of death. Nevertheless, minimal missing data may be inevitable.

As the primary approach, for the primary efficacy analysis with the mITT population, data will be assumed to be missing at random, with no data imputation. Sensitivity analysis with multiple imputations for missing primary endpoints will be conducted to assess whether the findings are consistent across alternative analysis approaches. We plan to use PROC MI and PROC MIANALYZE in the SAS software. A distribution for the primary outcome is derived from a logistic regression model that accounts for covariates assessed at baseline and clinical visits prior to Day 75. A random sample from this distribution is used to impute values for missing primary outcomes. Five sample data sets with complete efficacy endpoint are generated through PROC MI, and each of the data sets are analyzed according to the method described, and the results (regression parameter and covariance matrix estimates) for each sample are combined and analyzed with PROC MIANALYZE to derive a valid statistical inference about the treatment effect.

Missing data in secondary endpoints will be assumed missing at random and no data imputation will be used in secondary endpoints analyses.

8.7. ASSESSMENT TIME WINDOWS

The Baseline visit should occur within 28 days of the screening visit. For all scheduled visits, allowable visit windows and study procedures are ± 14 days from the calculated target day. The target day is defined as (Baseline Visit + 75 days) for the Day 75 target day, and (Baseline Visit + 365 days) for the Day 365 target day. If multiple measurements occur within the assessment time window, the measurement closest to the scheduled target day will be analyzed. Data collected outside of the specified time window will not be included in the primary analysis.

8.8. DESCRIPTIVE ANALYSES

Characteristics of studied patients (i.e., demographics, disease status, glucose & hba1c levels) and measures of study feasibility (i.e., enrollment refusal rate, proportion of enrolled subjects who are successfully transplanted) will be summarized using descriptive statistics (i.e., means, standard deviations, medians, percentages) and 2-sided 95% confidence intervals.

8.9. EFFICACY ANALYSES

The primary efficacy analyses will involve the use a general linear mixed model (GLMM) to test whether the primary endpoints differ over time between subjects assigned to the AAT arm when compared to subjects assigned to placebo. The analysis will be performed on the mITT and PP populations, although the analyses within the mITT population will be considered primary.

Contrasts will be constructed to estimate the AAT treatment effect on outcomes at day 75 and at day 365. To account for the fact that observations within the same subjects will be correlated, various error covariance structures will be considered, including unstructured, autoregressive, and compound symmetry. If model assumptions are not met (e.g. normality) alternative strategies will be utilized, including transformations of dependent variables and non-parametric alternatives. Any pre-transplantation subject characteristics be found to be significantly different between the study subjects and historical controls will be included as covariates for all between-group comparisons. Model fit will be assessed using criteria such as Akaike Information Criterion. All primary and secondary outcomes will be reported in study communications.

8.10. SAFETY ANALYSES

Study subjects will be asked to report any and all AEs/new symptoms at any time from study enrollment until 52 weeks after study treatment, whether or not they attribute them to the study intervention or procedures. Subjects, who discontinue the study treatment regimen for any reason, including subjects who are treatment failures due to unable to return for some of the treatment injection(s) will be encouraged to attend the remaining visits for assessment of safety, secondary and pharmacokinetic endpoints.

To assess safety in this population, vital signs will be performed at each of the study visits. Additionally, medical history will be collected at screening and baseline and adverse events occurring after start of study therapy will be recorded.

Since the safety endpoints are primarily binary indicators for each subject (e.g. experiencing a particular AE during the 24-weeks post-treatment), their analyses will involve logistic regression models. For certain safety endpoints, it may be more appropriate for them to be analyzed using survival techniques, which are more suitable for time-to-event data than logistic regression. In such circumstances, Cox proportional hazards models will be used to compare treatment arms; however, should the proportionality assumptions not hold, alternative strategies (e.g. stratified analyses) will be used. The safety analyses will be conducted in the Safety Population.

8.11. SECONDARY EFFICACY ANALYSIS

A series of secondary efficacy and exploratory endpoints will be evaluated, as listed in Section 3.5.2 and 3.5.3. All secondary analyses will be conducted in an exploratory fashion with p-values and confidence intervals presented with no adjustments for multiple comparisons. Interval estimates will be generated at the 95% confidence level. Secondary analyses will be conducted on the mITT population and the per protocol population. Since most secondary endpoints will be collected at multiple time points for each participant, generalized linear mixed models will be utilized, as they are appropriate for longitudinal data analyses and can be adapted for binary dependent variables.

Secondary endpoints analyses are used to confirm or support the findings based on the primary outcome analysis. If most of the secondary endpoints show a change in the opposite direction

from the primary efficacy analysis or no direction, we might have less confidence in the primary endpoint.

8.12. MECHANISTIC ANALYSIS

Since many of the mechanistic endpoints will be collected at multiple time points for each participant, statistical models appropriate for longitudinal data analyses will be used. For example, serum samples for cytokines will be collected at Baseline, day 1, 3, and 7 days post transplantation. The GLMM used to compare treatment groups will be of the form:

$$Kynurenine_{ij} = \alpha + \beta_1 \cdot Treatment_i + \beta_2 \cdot Kyn_0 + \beta_3 Week_j + \gamma_i + \gamma_{ij} \cdot Week_j + \epsilon_{ij}$$

This GLMM example treats cytokine as the dependent variable, including fixed effects for treatment group, baseline cytokine, and week, along with random subject intercepts (γ_i) and random subject slopes (γ_{ij}). Link functions appropriate for each dependent variable (i.e. each mechanistic outcome) will be selected, depending on its distributional form. Similar models will be constructed for other mechanistic endpoints.

9. QUALITY CONTROL AND QUALITY ASSURANCE

The investigator is required to keep accurate records to ensure that the conduct of this study is fully documented, and to ensure that CRFs are completed for all subjects according to the study guidelines outlined in the study protocol and database training materials. As part of the quality assurance and legal responsibilities of an investigation, the study site permit authorized representatives of the sponsors and health authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews, audits, and evaluations of the study safety and progress. Unless required by the laws that permit copying for recorders, only the coded identity associated with documents or with other subject data may be copied (and all personally identifying information must be obscured). Authorized representatives as noted above are bound to maintain the strict confidentiality or medical and research information that is linked to identified individuals.

Results of all clinical and laboratory evaluations will be maintained in the subject's medical records and the data will be transferred from these source documents directly to the study data base. All data will be entered/imported, stored, and managed in an encrypted database. Access to data entry screens will be user ID and password protected. Each user will be provided with a unique personal ID and password. The Data will be verified for missing data, inconsistencies, and for any necessary medical clarifications. All relevant data queries arising from these checks will be sent to the Investigator for response and signature. After all data is confirmed, it will be locked for further analysis.

In addition, prior to study initiation, current, signed and dated curriculum vitae, CITI training certificates, and financial disclosure statement of PI and co-investigators will be gather in the regulatory binder, and information will be updated at least every two years.

10. PROTOCOL DEVIATIONS/AMENDMENTS

Any amendment will be sent to the appropriate IRB. No deviation from or changes to the protocol will be implemented without documented approval of an amendment from the IRB which granted the original approval, except where necessary to eliminate an immediate hazards to trial patient, or only when change(s) involves only logistical or administrative aspects of the trial. The deviation and the proposed amendment, if appropriate, should be submitted to the IRB for review and approval as soon as possible.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the IRB, and inspections by applicable regulatory authorities. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses.

12. ETHICAL CONSIDERATION AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

12.1. Statement of Compliance

The clinical study will be conducted using cGCP, as stated in Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by IRB, and submitted to the DSMB board through the NIH/NIDDK. Any amendments to the protocol or the consent materials must be approved by the IRB before implemented, and the amendments will be reported to the sponsor.

12.2. Informed Consent

The informed consent for research to be ethical, most agree that individuals should make their own decision about whether they want to participate or continue participating in research. This is done through a process of informed consent in which individuals (1) are accurately informed of the purpose, methods, risks, benefits, and alternatives to the research, (2) understand this information and how it relates to their own clinical situation or interests, and (3) make a voluntary decision about whether to participate.
The informed consent must be revised whenever important new safety information is available, whenever the protocol is amended, and or whenever any new information becomes available that may affect participation in the trial.

12.3. Privacy and Confidentiality

Each patient will be assigned a unique identification number, and used for data collection, store and reporting subject information. Subjects' privacy and confidentiality will be respected throughout the study.

13. PUBLICATION POLICY

Any publication of study results will adhere to the NIH Public Access Policy.

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APPENDIX 1:

Study Phase	**Screening**	**Treatment**									**Premature Withdrawal**
Time points (days relative to transplant)	**Screening**	**Baseline Before Surgery**	**Baseline After/ During Surgery**	**Day 1**	**Day 3**	**D7**	**D14**	**D21**	**D75**	**D365**	
Visit#	1	2				**3**	**4**	**5**	**6**	**7**	
Visit Windows (days)						±2	±2	±2	±15	±15	
Informed Consent	x										
Medical and Diabetes History	x					x	x	x	x	x	**x**
Inclusion/Exclusion	x										
Immunoglobulin A (IgA)	x										
AAT infusion		x				**x**	**x**	**x**			
TP-IAT			x								
Inflammatory Cytokine Levels		x	x[3]	x	x	x	x	x			
TAT, C3a, c-pep		x	x[1], x[2]								
Serum AAT level		X[4]									
Blood mononuclear RNA		x				x					
Blood DNA		x									
Plasma for proteomics, siRNA, etc		x				x					
MMTT -240min c-peptide and glucose									x	x	
Adverse Event Recording		x	x	x	x	x	x	x	x	x	x

1 Time 0 and 15 minutes after initiation of islet cell infusion in radiology suite.
2 Time 3 hours after initiation of islet cell infusion when participant is back in ICU.
3 Cytokine profile obtained 24 hours after initiation of islet cell infusion when participant is back in ICU.
4 AAT levels will be measured prior and 30mins after the first AAT infusion.

APPENDIX 2:

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