A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED STUDY OF THE EFFECTIVENESS OF CHRONIC INCRETIN-BASED THERAPY ON INSULIN SECRETION IN CYSTIC FIBROSIS

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Study Product: *Sitagliptin(Januvia®)*

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List of Abbreviations

ADA	American Diabetes Association
AE	Adverse event
β-cell	Pancreatic Beta-cell
BMI	Body Mass Index
CHOP	The Children's Hospital of Philadelphia
CF	Cystic Fibrosis
CFRD	Cystic Fibrosis Related Diabetes
CFTR	Cystic Fibrosis Transmembrane Regulator
CTRC	Clinical and Translational Research Center
FH	Fasting Hyperglycemia
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1	Glucagon-Like Peptide-1
GPA	Glucose Potentiated Arginine
IDS	Investigational Drug Services
IGT	Impaired Glucose Tolerance
Ind-GT	Indeterminate Glucose Tolerance
MMTT	Mixed Meal Tolerance Test
NGT	Normal Glucose Tolerance
OGTT	Oral Glucose Tolerance Test
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
TCF7L2	Transcription Factor 7–Like 2
UPenn	University of Pennsylvania

Study Summary

Title	*A Randomized, double-blind, placebo controlled study of the effectiveness of chronic incretin-based therapy on insulin secretion in cystic fibrosis*
Short Title	*Effects of chronic incretin therapy in cystic fibrosis*
Protocol Number	*818014*
Phase	*Mechanistic*
Methodology	*Randomized, double blind, placebo controlled study of the effect of the DPPIV inhibitor sitagliptin that raises endogenous levels of incretin hormones on the second-phase insulin response derived from a glucose-potentiated arginine test.*
Study Duration	*44 months*
Study Center(s)	*Single-center*
Objectives	*To determine effectiveness of chronic incretin-based therapy vs. placebo on insulin secretion in cystic fibrosis patients with indeterminate glucose tolerance, impaired glucose tolerance, or cystic fibrosis related diabetes.*
Number of Subjects	*36*
Diagnosis and Main Inclusion Criteria	Confirmed diagnosis of cystic fibrosis, defined by positive sweat test or CFTR mutation analysis. Age ≥18 years on date of consent, pancreatic insufficiency and recent OGTT consistent with indeterminate, impaired, or diabetic glucose tolerance without fasting hyperglycemia.
Study Product, Dose, Route, Regimen	*Sitagliptin (Januvia®) 100mg by mouth daily*
Duration of administration	*6 months*
Reference therapy	*Placebo*
Statistical Methodology	The change in second-phase insulin response derived from the glucose-potentiated arginine test will serve as the primary outcome measure and be compared between the groups receiving sitagliptin or placebo using two-group Mann-Whitney methods.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

As life expectancy improves in individuals with cystic fibrosis (CF), CF-related co-morbidities are receiving increasing attention —they not only impose additional medical burden but may also compromise pulmonary health. CF-related diabetes (CFRD) is one such co-morbidity: an estimated 26% of 10-20 year olds and 40-50% of adults with CF have CFRD(1,2). Risk factors include female sex, pancreatic insufficiency and ΔF508-homozygous genotype(3-5).

CFRD is associated with up to a 6-fold greater mortality (6). In the 1980's, <25% of CFRD patients survived to age 30 years compared to 60% of non-diabetic CF subjects(7). CFRD is also associated with worse clinical status as indicated by worse pulmonary function, increased acute pulmonary exacerbation rates, greater prevalence of important sputum pathogens, and poorer nutritional status(4). Gradual BMI and lung function decreases may occur up to 4-years prior to CFRD diagnosis(8).

The mechanisms linking CFRD with worse outcomes are not fully delineated, but likely involve direct damaging effects of hyperglycemia as well as catabolism promoted by insulin insufficiency. The negative impact of CFRD on nutrition is underscored by the decreased 5-year survival in the general CF population with ideal body weight <85% versus those with ideal body weight >85%(9). Moreover, the rate of pulmonary deterioration over a 4-year period correlates with the degree of insulin deficiency at baseline(10). These findings reinforce the link between loss of insulin's potent anabolic effects and clinical deterioration(11).

Importantly, insulin therapy improves nutritional status and pulmonary function in people with CFRD and perhaps even in those with less severe defects in glucose regulation. Small studies suggest insulin therapy improves or stabilizes pulmonary function and augments nutritional status in CFRD(12,13) and in CF patients with deteriorating clinical status but elevated casual blood glucose despite normal oral glucose tolerance tests (OGTT)(14). A randomized trial found insulin therapy was associated with sustained BMI increases in subjects with CFRD without fasting hyperglycemia(15)—suggesting earlier CFRD intervention may have long-term benefit.

While the insulin deficiency that underlies development of CFRD has traditionally been considered a product of "collateral damage" (pancreatic exocrine damage extending to pancreatic islets), new evidence points to similarities between CFRD and the insulin secretion defects of T2D:

- Retrospective immunohistochemical studies of islets from patients with CF suggest reductions in β-cell mass are variable and do not correlate with the diagnosis of CFRD (16-18).
- Reductions in β-cell mass are found in obese and lean adults with T2D(19).
- Deposition of islet amyloid, a β-cell apoptosis mediator and endoplasmic reticulum stress marker, is found in CFRD, CF-related impaired glucose tolerance (IGT)(20), and T2D but in neither T1D nor diabetes of chronic pancreatitis(21).
- Twin studies suggest genetic modifiers play a substantial role in CFRD(22), most obviously by a variant in the gene harboring transcription factor 7–like 2 (TCF7L2)*(23)*. These variations within *TCF7L2*(24-26) are also the strongest genetic associations with T2D reported to date, and furthermore are robustly associated with T2D in all major racial groups(27-42)
- Decreased secretion of incretins(43), hormones secreted by small intestine endocrine cells in response to nutrients, and impaired incretin-augmented insulin secretion(44) are found in T2D and potentially in CF(45).
- Decreased incretin-stimulated insulin secretion (via direct effect (46,47) or at the receptor level(48,49)) and impaired conversion of pro-insulin to insulin(50) may underlie the link between *TCF7L2* variants and T2D.

Because of the possible link between insufficient incretin action and impaired insulin secretion in CFRD as in T2D, the present study will determine whether early intervention with incretin-based therapy using the DPP-4 inhibitor sitagliptin (Januvia®) to raise endogenous levels of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotrophic polypeptide (GIP) for a 6 month period will improve insulin secretion in CF patients with indeterminate glucose tolerance, impaired glucose tolerance or early CFRD.

1.2 Investigational Agent

Sitagliptin (Januvia®) is an oral DPP-4 inhibitor approved in 2006 for treatment of Type 2 Diabetes. Daily dosing of 100 mg sustains ≥ 80% inhibition of DPP4 and results in ≥ 2-fold increases in levels of active GLP-$1_{7\text{-}36\ amide}$ and GIP following meal ingestion (51,52). These actions are associated with enhanced glucose-dependent insulin secretion and glucagon inhibition as seen with GLP-1 administration, but without marked effects on satiety or gastric emptying. Thus, DPP-4 inhibition provides similar glucose lowering, and is better tolerated than presently available GLP-1 analogs without affecting body weight (53,54).

1.3 Clinical Data to Date

Please refer to appendix 1 for sitagliptin (Januvia®) labeling.

1.4 Dose Rationale and Risk/Benefits

The dose of sitagliptin (Januvia®) will be 100 mg orally each morning. Hypoglycemia is not expected with the use of sitagliptin alone because its effects on insulin secretion are glucose dependent; nonetheless, incidence of hypoglycemia will be carefully monitored by recommended twice daily glucose monitoring on a study glucometer provided to the subjects. Subjects with CFRD who may be receiving oral hypoglycemic agents or insulin therapy and performing more frequent glucose monitoring will have their oral agent or insulin doses assessed throughout their participation and adjusted as needed to avoid hypoglycemia. A rare association between sitagliptin use and pancreatitis has been reported by the FDA from post-marketing surveillance. However, the documented rate of pancreatitis occurring among patients treated with sitagliptin is 0.10%, which is comparable to control cohorts (RR 1.0, 95% CI 0.5-2.0), making the likelihood of such an event extremely unlikely in this trial (55). Nevertheless, subjects will be instructed to immediately stop the study medication and contact the Principal Investigator with the development of any abdominal pain. Rare post-marketing reports of hypersensitivity reactions have also been reported with sitagliptin use. Subjects will receive their first dose under observation in the Clinical & Translational Research Center, and be instructed to immediately stop their study medication and contact the Principal Investigator with the development of any rash or swelling.

2 Study Objectives

Primary Objective
To determine effectiveness of chronic incretin-based therapy vs. placebo on insulin secretion in CF patients with indeterminate glucose tolerance, impaired glucose tolerance, or CFRD.

Primary Hypothesis: Exposure to the dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin, which inhibits enzymatic cleavage of incretin hormones and raises levels of endogenous GLP-1 and GIP, will improve β-cell sensitivity to glucose as well as glucose excursion and insulin secretion during a mixed meal.

The effect of chronic incretin-based therapy on β-cell sensitivity to glucose, β-cell secretory capacity, and glucose excursion and insulin secretion during a mixed meal tolerance test will be evaluated using a randomized, placebo-controlled, double-blind clinical trial of 6 months duration. The role of incretins in insulin secretion defects in CF is poorly defined. To capture early insulin secretion defects, subjects with indeterminate glucose tolerance (Ind-GT) and impaired glucose tolerance (IGT) will be studied in addition to those with early CFRD defined by the absence of fasting hyperglycemia (FH). The glucose-potentiated arginine (GPA) test will be used as the “gold-standard” assessment of β-cell secretory capacity and

sensitivity to glucose, measures of β-cell mass and function. The mixed meal tolerance test (MMTT) will be used to assess incretin secretion since fat is an important secretagogue for GLP-1 and gastric inhibitory polypeptide GIP and, in the setting of pancreatic insufficiency, incretin secretion may be compromised even with appropriate pancreatic enzyme replacement therapy.

Exploratory Objective
To compare β-cell secretory capacity and incretin secretion in non-diabetic CF subjects homozygotes for either the TCF7L2 T2D-conferring T allele or the wild-type C allele of SNP rs7903146.

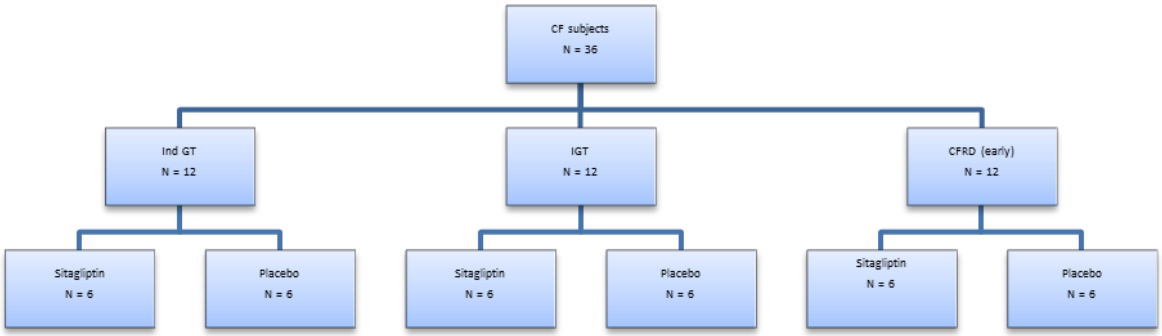
Exploratory Hypothesis: Nondiabetic CF subjects homozygous for the TCF7L2 T2D-conferring T allele have reduced β-cell secretory capacity and decreased incretin secretion compared to non-diabetic subjects homozygous for the wild-type C allele.

Genotyping of *TCF7L2* and the approximately top ten other T2D GWAS-implicated genes is being performed in individuals from the Adult and Pediatric CF Centers, and the association of these genotypes with measures of insulin and incretin secretion derived from the current study will be examined. We will also extend our understanding of the *TCF7L2* locus in CFRD by performing functional studies of insulin and incretin secretion as a function of *TCF7L2* genotype. These studies in a CF population whose metabolic phenotype is carefully delineated will provide additional insights into CFRD risk and potential mechanisms.

3 Study Design

3.1 General Design

The Cystic Fibrosis Foundation recommends annual screening for CFRD using the two hour OGTT, and four glucose tolerance groups can be defined (normal, Indeterminate: 1-hr OGTT plasma glucose ≥ 155 mg/dL and 2-hr OGTT plasma glucose < 140 mg/dL, impaired glucose tolerance: 2-hr OGTT plasma glucose 140-199 mg/dL, CFRD 2hr OGTT plasma glucose ≥ 200mg/dL). As pictured below, pancreatic insufficient CF subjects (n=36) will be recruited: 12 with indeterminate glucose tolerance, 12 with impaired glucose tolerance, and 12 with CFRD without fasting hyperglycemia (FH). All subjects will be randomized to two groups of 18 (6 months of sitagliptin 100 mg daily or placebo therapy). Glucose-potentiated arginine test and a mixed meal tolerance test will be obtained at baseline and following 6 months of therapy.



3.2 Primary Study Outcome

The primary outcome measure will be the change in second-phase insulin response derived from the glucose-potentiated arginine test as a measure of β-cell sensitivity to glucose.

3.3 Secondary Study Outcomes

Secondary outcome measures will include the PG_{50}, another measure of β-cell sensitivity to glucose, and AIR_{max}, a measure of β-cell secretory capacity, both derived from the glucose-potentiated arginine test, and glucose excursion, and insulin, glucagon and incretin (GIP, GLP-1) secretory responses calculated from incremental AUCs derived from the mixed meal tolerance test.

An exploratory outcome measure will be presence of the T2D risk-conferring SNP rs7903146 in *TCF7L2*.

3.4 Primary Safety Outcomes

The primary safety outcomes will be the occurrence of any severe hypoglycemia episode requiring assistance of another person for correction, the occurrence of any episode of pancreatitis, and the occurrence of any hypersensitivity reaction.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1) Confirmed diagnosis of CF, defined by positive sweat test or CFTR mutation analysis according to CFF diagnostic criteria, 2) age ≥ 18y on date of consent, 3) pancreatic insufficiency, 4) recent OGTT consistent with Indeterminate-GT, IGT, CFRD w/o fasting hyperglycemia, or an established diagnosis of CFRD without fasting hyperglycemia, 5) for female subjects, negative urine pregnancy test at enrollment.

4.2 Exclusion Criteria

1) Established diagnosis of non-CF diabetes (i.e. T1D) or CFRD with fasting hyperglycemia, (fasting glucose > 126 mg/dL) 2) history of clinically symptomatic pancreatitis within last year, 3) prior lung or liver transplant, 4) severe CF liver disease, as defined by portal hypertension, 5) fundoplication-related dumping syndrome, 6) History of any illness or condition that, in the opinion of the investigator might confound the results of the study or pose an additional risk to the subject, 7) acute CF Pulmonary exacerbation within 4 weeks prior to enrollment, 8) treatment with oral or intravenous corticosteroids within 4 weeks of enrollment, 9) hemoglobin <10g/dL, within 90 days of GPA test or at Screening, 10) abnormal renal function, within 90 days of GPA test or at Screening; defined as Creatinine clearance < 50 mL/min (based on the Cockcroft-Gault formula) or potassium > 5.5mEq/L on non-hemolyzed specimen, 11) a history of anaphylaxis, angioedema or Stevens-Johnson syndrome, 12) Inability to perform study specific procedures (MMTT, GPA), 13) Subjects, who in study team opinion, may be non-compliant with study procedures, 14) Elevation of serum amylase or lipase > 1.5x ULN within 90 days of GPA test.
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4.3 Subject Recruitment and Screening

Potential subjects will be identified by the study team from The Children's Hospital of Philadelphia (CHOP)-UPenn Cystic Fibrosis Center. The CF National Registry (approved by both Institutional IRB's) will be utilized to perform initial queries based on study inclusion/exclusion criteria. Currently, there is a CHOP-Penn Cooperative Agreement in place for the CF Center, to facilitate clinical research between both institutions. Recruitment flyers will also be posted in both CHOP and UPenn CF Centers. Directors of CF centers across the country will be notified about this study and asked to provide basic study details and study team contact information for any study interest in their patients. No contact will be made with potential subjects until approval has been obtained by their primary CF physician.

Enrollment is estimated to take approximately 36 months to complete. It is expected that approximately 36 subjects will be enrolled.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study protocol. The Investigator may also withdraw subjects to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

In the event of withdrawal before completion of the study protocol, data obtained until the time of withdrawal will be collected and may be used in the final analysis.

5 Study Drug

5.1 Description

Sitagliptin (Januvia®) is an oral DPP-4 inhibitor approved in 2006 for type 2 diabetes to improve glycemic control.

5.2 Treatment Regimen

Subjects will be randomized to daily dosing of 100 mg tablets of sitagliptin for 6 months or a matching placebo.

5.3 Method for Assigning Subjects to Treatment Groups

Subjects will be randomized equally to two groups of 18 (Sitagliptin 100 mg daily vs. placebo). Sitagliptin and placebo will be prepared by Merck and distributed by CTRC Investigational Drug Services (IDS). Randomization will be performed centrally by the project statisticians and implemented using opaque sealed envelopes to ensure allocation concealment. Balance between treatment arms will be maintained by use of randomly permutated blocks with unequal block sizes and with stratification by glucose tolerance (Ind-GT, IGT, CFRD w/o FH).

5.4 Preparation and Administration of Study Drug

Merck Sharp & Dohme Corp., a subsidiary of Merck & CO., INC., will prepare sitagliptin 100mg tablets and matching placebo tabletes. Drug and placebo will be distributed by IDS. Patients will be randomized to receive sitagliptin (Januvia®) or placebo, which will be self-administered by the patient once daily in the morning.

5.5 Subject Compliance Monitoring

Patients will be asked to bring study medication to each visit for a dose count. Pill counts, monthly calendars for charting, and completion of Adherence Questionnaire, a semi-structured interview by study staff with families by phone monthly to review adherence. Pill counts will begin at visit 3 (1 month follow-up) and continue through all subsequent visits. If a patient is found to have reduced compliance (defined as < 80% expected), a member of the study staff will phone the patient on a regular basis to remind the patient to take his/her study medication.

5.6 Prior and Concomitant Therapy

At the time of the screening visit, subjects will be asked about all prior medications and all medications used within 45 days prior to enrollment will be recorded. Subjects will be on a stable regimen of CF medications at study entry. Subjects with CFRD w/o FH will hold short acting hypoglycemic medications (e.g. Prandin® or aspart insulin) for 12 hours before each study test (GPA or MMTT), coinciding with fasting time and will hold long acting hypoglycemic medications (e.g., glargine insulin) for 24 hours before

each study test. Subjects with CFRD will continue their usual home insulin regimen. Sitagliptin therapy may lower insulin requirements. Blinded study staff will contact all subjects 5-7 days after treatment initiation to review BG and adjust insulin doses as needed. Insulin to carbohydrate ratios and correction factors will be recorded for CFRD subjects at baseline, following 5-7 days of therapy, and at each study visit.

Intercurrent illness, hospitalization, and use of systemic glucocorticoids are not uncommon in individuals with CF. These episodes can be accompanied by worsening of glucose tolerance and the need for insulin therapy (transient or permanent). We will continue therapy through these episodes and study subjects at least 6 weeks beyond illness resolution to minimize the impact of illness on insulin secretion. Progression to CFRD or from CFRD without fasting hyperglycemia to with fasting hyperglycemia will be noted (but patient numbers will limit ability to compare events between treatment groups).

5.7 Packaging

Sitagliptin 100mg and placebo are supplied as beige, round, film-coated tablets directly from the manufacturer, Merck.

5.8 Blinding of Study Drug

Once the request for treatment allocation is received, the CTRC pharmacist will open the sealed envelope, assign the subject to the designated therapy, and prepare a log which maps subject to study number. Successful assignment will be reported to the project statistician. Neither the patients nor treating physicians will have access to treatment assignment, until the subject has completed the period of observation or unless a clinical emergency or adverse event requires unblinding of treatment assignment.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Upon receipt of the of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator will notify Merck of any damaged or unusable study treatment supplies.

5.9.2 Storage

All medications will be stored by Investigational Drug Service at the University of Pennsylvania in a secure location. Sitagliptin and placebo will be at room temperature, light protected, and in a tightly closed container. A member of the Investigational Drug Service staff will monitor the study medication storage area for temperature consistency. Documentation of temperature monitoring will be maintained.

5.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team. All subjects will receive a patient medication information sheets upon randomization.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Hemoglobin A1c

Will be measured in HUP Clinical Lab at baseline, 3 months and 6 months

6.2 Complete blood count, amylase and lipase, comprehensive metabolic panel

Will be measured in HUP Clinical Lab at baseline, 1 month, 3 months, and 6 months.

6.3 Anthropometry

Weight measured by digital electronic scale (Scaletronix) and stature on a stadiometer (Holtain). BMI will be calculated. Age- and sex-specific Z-scores will be generated.

6.4 Spirometry (Pulmonary Function tests)

Spirometry are routinely collected in CF patients >6 years and recorded in PortCF, the national CF database. Forced vital capacity (FVC) and FEV1 are measured using standard techniques(56). At least three acceptable maneuvers are performed until two reproducible values (American Thoracic Society criteria) are obtained. The highest value is documented. Values are reported as a percent of predicted based upon gender, height, weight, and race using NHANES III prediction equations. PFT data will be obtained from the Pulmonary outpatient chart or PortCF database from the 6 months prior to enrollment through the intervention.

6.5 Genotyping:

SNP genotyping of rs7903146 in TCF7L2 will be carried out by standard TaqMan® genotyping methodologies at the CHOP Center for Applied Genomics (Associate Director, Struan Grant PhD; Study Co-Investigator). Approximately 6 ml of blood will be obtained from the subject for this genotyping. Primers and probes are already available from ABI (Applied BioSystems). Each reaction will be completed in a total volume of 20 µLcontaining 1x ABI TaqMan® Master mix, 0.9 mM of each primer and 0.25 mM probe with ~25ng of DNA. Reactions will then be carried out in 384-well plates using the following parameters: one cycle of 50ºC for 2 minutes, 95ºC for 10 minutes, followed by 40 cycles of 95ºC for 15 seconds and 60ºC for 1 minute. Each reaction will be performed in triplicate. A similar approach will be used for genotyping GWAS-implicated T2D variants in CAPN10, HNF1B, FOXO1, WFS1, SGK1, KCNQ1, SLC30A8, CDKAL1, IGF2BP2, MTNR1B(56,57).

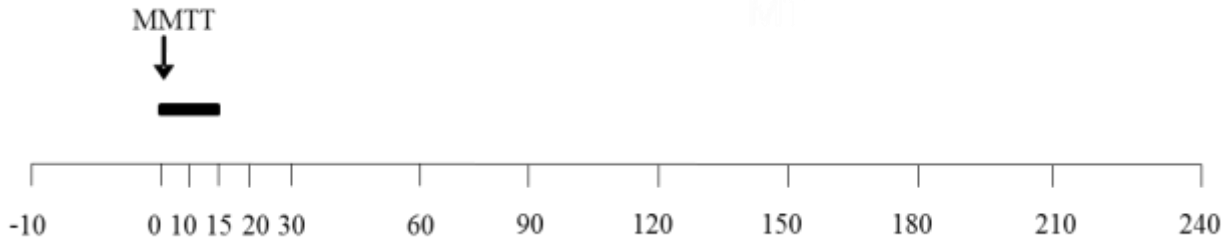
6.6 Mixed Meal Tolerance Test

Glucose excursion, insulin secretion and incretin secretion in response to a meal will be evaluated during a mixed meal tolerance test. A mixed-meal test offers the potential for not only assessing glucose tolerance but also insulin secretion during physiologically relevant situations and for evaluating the physiologic effects of incretins.
Subjects will be admitted to the CTRC of UPenn the evening prior to the study and will fast after 20:00. If preferred and reasonable, a subject may fast overnight at home, and arrive in the CTRC by 07:00. At 07:00, subjects will have an antecubital intravenous catheter placed for blood sampling, with the arm placed in a heating pad to promote arterialization of venous blood. Patency of the catheter will be maintained with a slow infusion of 0.9% normal saline. Morning medications will be held until 12:00, with the exception of pancreatic enzymes (see below).

Following 12-hours of overnight fasting and baseline blood sampling at -10 and 0 minutes, subjects will consume an 820 kcal breakfast over 15 minutes. The carbohydrate, fat and protein content of the meal composition will be 47%, 40%, 13% of the total energy content. The CF or CTRC dietitian will assist the

subject in selecting the contents of the meal. This consultation may occur by phone prior to admission to the CTRC. Subjects will take their pancreatic enzymes with the test meal. Blood samples will be obtained at baseline -10, 0, +10, +15, +20 and every 30 minutes for 4 hours after consumption of the meal. Total blood sampling during the mixed meal tolerance test will involve approximately 65 ml. After collection, protease inhibitor cocktail and a DPPIV inhibitor (Sigma Aldrich, St. Louis, MO) will be immediately added to the blood samples. Samples will then be placed on ice, centrifuged at 4 C and frozen at -80C until biochemical analysis.

Visit 1 and 5: Blood draws during the mixed meal tolerance test (MMTT) after 12 hours of fasting



Biochemical Analysis
Plasma glucose will be determined in duplicate on an YSI 2300 automated glucose analyzer (Yellow Springs, OH) in the CTRC at HUP. Plasma immunoreactive insulin, C-peptide and glucagon will be measured in duplicate by double-antibody radioimmunoassays purchased from Millipore (Billerica, MA) and performed at the Diabetes Research Center (DRC) at UPenn. GLP-1 and GIP will be measured in duplicate by enzyme-linked immunosorbent assays purchased from Millipore and performed at the CHOP CTRC Biochemistry lab.

6.7 Glucose Potentiated Arginine Test

The GPA test will be performed at baseline and after 6 months of incretin-based therapy. Measures of β-cell responsiveness will be derived from a glucose potentiated arginine (GPA) test conducted by Dr. Michael Rickels, a trained nurse practitioner, or a trained endocrinology fellow. Testing for pre-menopausal women will be attempted during the first 14 days of their menstrual cycle.

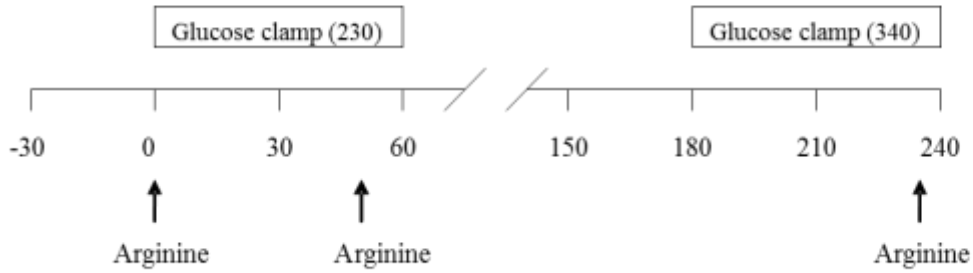
Subjects may be admitted to the CTRC of UPenn the evening prior to the study and will fast after 20:00. If preferred and reasonable, a subject may fast overnight at home, and arrive in the CTRC by 07:00. At 07:00, subjects will have an antecubital intravenous catheter placed for infusions, and a contralateral intravenous catheter placed for blood sampling. The blood sampling catheter will be placed in a retrograde fashion in a dorsal hand vein, and the hand placed in a thermo-regulated box (warmed up to 40-degrees centigrade) or heating pad to promote optimal arterialization of venous blood. Patency of the intravenous catheters will be maintained with a slow infusion of 0.9% normal saline. Morning medications will be held until 12:00.

Baseline blood sampling will occur at -5 and -1 minutes. The baseline arginine stimulated test (AST) will be performed at t = 0 with 5g arginine hydrocholoride (50mL 10% solution) injected over a 1-minute period. Blood samples will be collected at 2, 3, 4 and 5 minutes post-injection.

At t = 10 min after the baseline arginine stimulation test (AST) above, a hyperglycemic clamp technique utilizing a variable rate of a 20% dextrose solution will be performed to achieve a plasma glucose level of 230 mg/dL. Blood samples will be taken every five minutes, spun, and measured at the bedside by an automated glucose analyzer (YSI 2300), and used to adjust the infusion rate to achieve the desired

glucose level. After 45-min of the dextrose infusion, the 5 g arginine pulse will be injected again with identical blood sampling. Then a 2-hour period without dextrose infusion will take place to avoid the priming effects of hyperglycemia on insulin release. The plasma glucose will be monitored every 10 min for the first 30 min and then at least every 30 min until the end of the period, and if the plasma glucose decreases to ≤ 65 mg/dl the dextrose infusion will be resumed to normalize the glucose level ≥ 70 mg/dl. At the end of the 2-hour period, a hyperglycemic clamp will be performed to achieve a plasma glucose level of 340 mg/dL. Forty-five minutes after the initiation of the dextrose infusion, another arginine pulse will be injected with identical blood sampling. Blood sampling during the GPA test will involve approximately 90mL. Immediately after collection of each blood sample, protease inhibitor cocktail (Sigma Aldrich) will be immediately added and these will then be placed on ice, centrifuged at 4 C and frozen at -80C until biochemical analysis.

Visit 2 and 6: Glucose Potentiated Arginine (GPA) test



Biochemical Analysis
Plasma glucose will be determined in duplicate on an YSI 2300 automated glucose analyzer in the CTRC at HUP. Plasma immunoreactive insulin, C-peptide, and glucagon will be measured in duplicate by double-antibody radioimmunoassays purchased from Millipore and performed at the UPenn DRC. Additional plasma will be stored for potential analysis of proinsulin and amylin.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Visit	Screening	Baseline Visit 1	Baseline Visit 2	1 MO* Visit 3	3 MO* Visit 4	6 MO Visit 5	6 MO Visit 6
Informed consent	X						
Review Inclusion/Exclusion Criteria	X						
Demographics/Medical and Medication History	X			X	X	X	
Brief Physical Examination	X				X	X	
Vital Signs: BP, HR, RR	X	X	X		X	X	X
Height and Weight	X	X	X		X	X	X
Urine Pregnancy Test (if applicable)[1]	X	X		X	X	X	
Comprehensive Metabolic Panel	X[2]			X	X	X	

Amylase and lipase	X[2]			X	X	X	
Complete blood count	X[2]			X	X	X	
Oral Glucose Tolerance Test [6]	X						
Adverse Event Assessment	X	X	X	X	X	X	X
HbA1c level		X			X	X	
Pulmonary Function tests	X[2]				X[3]	X[3]	
Mixed Meal Tolerance Test		X[4, 5]				X	
Genotyping for TCF7L2		X[4]					
Glucose Potentiated Arginine (GPA) test			X[4, 5]				X

[1]Will be repeated upon each new admission to the CTRC.
[2]Unless completed within 90 days of baseline GPA test.
[3]Unless completed within 30 days of visit.
[4]Unless completed within 30 days of screening as part of participation in IRB protocol #817585, "Determination of β-cell responsiveness to the incretin hormones GLP-1 and GIP in cystic fibrosis".
[5] MMTT and Baseline GPA may be switched due to scheduling capabilities
[6] Only if not completed within the last 6 months as part of routine care
*For convenience of subjects, safety labwork can be completed at local labs and physical exam/ height/weight information may be obtained from a routine CF clinic visit

6.8 Screening

After the consent process is completed, the following screening procedures will be performed:

- Collect demographic information
- Medical history (including Medications)
- Brief Physical Exam
- Vital Signs after being seated for 5 mins (including HR, RR, BP)
- Weight and Height measurement (without shoes)
- Urine Pregnancy test for females
- Collection of blood samples for clinical laboratory assessments (Comprehensive Metabolic Panel and Complete Blood Count, Amylase, Lipase); if not completed within 90 days of GPA test
- Oral glucose tolerance test; if not completed within the last 6 months as part of routine care
- Pulmonary Function tests; if not completed within 90 days of screening

The Study team will ensure that all inclusion/exclusion criteria are met before proceeding with the study procedures.

6.9 Baseline Visit 1

- Fasting begins at 8pm the evening before the visit. Subjects are allowed to drink water.
- Overnight stay is mandatory for CFRD subjects on long acting insulin for whom overnight monitoring is required for medical safety; however other subjects are allowed to fast at home if preferred/feasible. This is with the understanding that fasting must continue until the next morning, at the CTRC, for the mixed meal tolerance test.
- Vital signs after being seated for 5 minutes (including HR, RR, BP)
- Weight and Height measurement (without shoes)

- Urine Pregnancy test if applicable
- Collection of blood sample for HbA1c level
- Collection of blood sample for Genotyping for T7CFL2
- Mixed Meal Tolerance Test with prescribed pancreatic enzymes

6.10 Baseline Visit 2

- Fasting begins at 8pm the evening before the visit. Subjects are allowed to drink water.
- As above, overnight stay is mandatory for CFRD subjects on long acting insulin for whom overnight monitoring is required for medical safety; however other subjects are allowed to be discharged to home if preferred/feasible. This is with the understanding that fasting must continue until the next morning, at the CTRC, for the glucose potentiated arginine (GPA) test.
- Vital signs after being seated for 5 minutes (including HR, RR, BP)
- Weight and Height measurement (without shoes)
- Glucose Potentiated Arginine (GPA) test

6.11 1 Month Visit 3

- Scheduled after 1 month after starting blinded study medication (sitagliptin or placebo)
- Urine Pregnancy test if applicable
- Collection of blood samples for clinical laboratory assessments (Comprehensive Metabolic Panel and Complete Blood Count, Amylase, Lipase)
- Pill count, review medications/intercurrent illnesses, insulin dose adjustments and review side effects and adherence

6.12 2 Month Phone Call

- Study team will contact subject via phone to ensure continued compliance with study medication and to capture any adverse side effects.

6.13 3 Month Visit 4

- Scheduled 3 months after starting blinded study medication (sitagliptin or placebo)
- Vital signs after being seated for 5 minutes (including HR, RR, BP)
- Weight and Height measurement (without shoes)
- Urine Pregnancy test if applicable
- Collection of blood samples for clinical laboratory assessments (HbA1c, Comprehensive Metabolic Panel and Complete Blood Count, Amylase, Lipase)
- Pulmonary Function tests
- Pill count, review medications/intercurrent illnesses, insulin dose adjustments and review side effects and adherence.

6.14 4 Month Phone Call

- Study team will contact subject via phone to ensure continued compliance with study medication and to capture any adverse side effects.

6.15 5 Month Phone Call

- Study team will contact subject via phone to ensure continued compliance with study medication and to capture any adverse side effects.

6.16 6 Month Visit 5

- Scheduled after completion of 6 months of blinded study medication (sitagliptin or placebo)
- Fasting begins at 8pm the evening before the visit. Subjects are allowed to drink water.
- As above, overnight stay is mandatory for CFRD subjects on long acting insulin for whom overnight monitoring is required for medical safety; however other subjects are allowed to be

discharged to home if preferred/feasible. This is with the understanding that fasting must continue until the next morning, at the CTRC, for the mixed meal tolerance test.
- Vital signs after being seated for 5 minutes (including HR, RR, BP, weight, BMI)
- Weight and Height measurement (without shoes)
- Collection of blood samples for clinical laboratory assessments (HbA1c, Complete Blood Count, Comprehensive Metabolic Panel, Amylase, Lipase)
- Urine Pregnancy test if applicable
- Pulmonary Function tests
- Mixed Meal tolerance test

6.17 6 Month Visit 6

- Scheduled at the completion of 6 months of sitagliptin or placebo
- Fasting begins at 8pm the evening before the visit. Subjects are allowed to drink water.
- As above, overnight stay is mandatory for CFRD subjects on long acting insulin for whom overnight monitoring is required for medical safety; however other subjects are allowed to be discharged to home if preferred/feasible. This is with the understanding that fasting must continue until the next morning, at the CTRC, for the glucose potentiated arginine (GPA) test.
- Vital signs after being seated for 5 minutes (including HR, RR, BP, weight, BMI)
- Weight and Height measurement (without shoes)
- Glucose Potentiated Arginine (GPA) test

7 Statistical Plan

7.1 Database Design, Data Collection and Management:

We will design and maintain a single data collection and management database using REDCap (Research Electronic Data Capture), a secure web-based clinical and research database. The database will incorporate range checks and between-variables consistency checks to ensure that errors are captured and corrected in real time. The database will be password-protected, stored, and backed up daily. REDCap allows for automated export procedures, including download to commonly used statistical packages (SAS, Stata, R). After export, all data will be rechecked by the project statisticians for incorrect or missing values.

7.2 Sample Size Determination

The study will proceed with 18 subjects each in the treatment and the control groups. Power calculations were performed to account for correlation of measures within subject over time and thus to take advantage of the efficiency of a pre-post design using both the function “sampsi” in Stata v 12.0 and the PASS 2011 software (Hintze, J. PASS 11. NCSS, LLC. Kaysville, UT, www.ncss.com; 2011). Assuming a strong, but not unreasonable, intra-class correlations of 0.7 and 0.65, power will range from 0.78 to 0.82 to detect a one-SD difference in the second-phase insulin response. Previous work from our group suggests that among normal subjects, one SD in this response equates to 0.06 (muU/ml)/(mg/dl)(58), and in unpublished data we have documented two-SD differences between groups of islet transplant recipients.

7.3 Statistical Methods

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). For the various study measures, means, standard deviations, 95% confidence intervals, medians, and minimum and maximum values (depending upon normality) will be tabulated and reported for all continuous outcome variables by study group. Outliers will be sought using graphical inspection.

Analyses
MMTT: Baseline, peak and nadir glucose, insulin, GIP, GLP-1, and glucagon will be determined for each subject; a number of change scores (e.g., change from baseline to peak) and AUC will be calculated.

GPA Test: The acute insulin response to arginine (AIR_{arg}), a measure of first-phase insulin release, is calculated as the mean of 2, 3, 4, and 5-minute insulin levels minus the mean of -5 and -1 minute insulin levels. The response during the 230 mg/dl glucose clamp enables determination of glucose potentiation of arginine-induced insulin release (AIR_{pot}) and is maximal during the 340 mg/dl glucose clamp (AIR_{max}); providing a measure of β-cell secretory capacity that estimates functional β-cell mass. Between 60-250mg/dl the magnitude of AIR_{arg} is a linear function of plasma glucose. The glucose-potentiation slope (GPS) is calculated as the difference in acute insulin responses at fasted and 230 mg/dl glucose levels divided by the difference in plasma glucose: (AIR_{pot} - AIR_{arg})/ΔPG. As a measure of second-phase insulin response and β-cell sensitivity to glucose, the difference between insulin levels during the 230 mg/dl glucose clamp and fasting will be divided by the difference in corresponding glucose levels. β-cell sensitivity to glucose will be further assessed as the PG_{50}, the PG level at which half-maximal insulin secretion is achieved, using the y-intercept (b) of the GPS to solve the equation $½(AIR_{max}) = (GPS \cdot PG_{50}) + b$.

The primary outcome measure will be the change in second-phase insulin response derived from the GPA test. This change represents the slope over time in two-dimensions of insulin (y) and glucose (x). Treatment effectiveness, the relative influence of sitagliptin on levels and slope of insulin to glucose, will be assessed using "as randomized" (intention-to-treat) analysis, in which the key contrast will be a nonparametric comparison of changes in slope over time. Differences in slopes over time will be estimated using two-group Mann-Whitney methods. To take advantage of improved efficiency in a statistical model that adjusts for subject-level covariates and to benefit from the strong correlation of slope within a subject over time, an alternative analysis will use linear regression models with the slope as the outcome, time (baseline and after intervention) and treatment as main effects, and time-by-treatment interaction as the estimate of interest. This model will use generalized estimating equation methods to obtain robust variance estimates that will account for possible non-normality of slope measures. Secondary analysis will adjust for non adherence to sitagliptin therapy. Using methods outlined by Nagelkerke(59) and extended to longitudinal settings by Small et al(60), we will estimate the impact of sitagliptin among those who adhered to therapy, without the bias inherent in as treated or per-protocol analyses. Adherence-adjusted methods will not likely change statistical significance of contrasts with placebo, but these methods will estimate the expected impact of therapy under ideal conditions.

7.4 Subject Population(s) for Analysis

Recruitment of 12 subjects per glucose intolerance group (Ind-GT, IGT and CFRD without FH) is planned.

Any subject who was randomized and received the protocol required study drug exposure and required protocol processing will be subjected to the study analysis – both for the primary analysis and any applicable secondary analyses.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of

cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately

8.3 Investigator reporting: notifying the Penn IRB

All adverse events that are not serious will be summarized and reported to the DSMB and the UPenn IRB annually at the time of the continuing review.
Reports of the following problems adverse events will be made to the DSMB and UPenn IRB within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time which in the opinion of the principal investigator is:

  Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the UPenn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the UPenn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.4 Unblinding Procedures

This is a double blind study. Should an unexpected serious adverse event occur, that can be attributed to the drug, e.g.—pancreatitis, a report will be sent to the DSMB and they will determine if unblinding is necessary.

8.5 Medical Monitoring

Drs. Rickels and Kelly will oversee the safety of this protocol. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the implementation of the data & safety monitoring plan below. A separate data & safety monitoring board will include a regular assessment of the number and types of serious adverse events.

8.5.1 Data Monitoring Board (DSMB)—Interim monitoring and analysis

A data safety monitoring board (DSMB) will be established: (1) to protect study patients, (2) to safeguard their interests, (3) to monitor the overall conduct of the trial, (4) to help protect the integrity of the trial and the data, and (5) to supervise the conduct of any interim analyses. Specific rules and protocols for all reviews will be established in a formal protocol, and approved by the DSMB in its charter, prior to the first DSMB meeting. The DSMB will work jointly with the trial statisticians and clinical investigators to establish specific criteria to accomplish its tasks. The DSMB will consist of at least three members including an endocrinologist, a pulmonologist with expertise in CF, and a senior faculty member with expertise in clinical research who will serve as chair.

In accordance with Good Clinical Practice (GCP) standards, the Project investigators will establish procedures for identifying classes of AEs, documenting them on an Adverse Experience Report (AER) form, and then reporting them regularly to DSMB.

The DSMB will meet annually to review efficacy issues and adverse events, and will have additional conference calls as needed. Annual reports will be prepared for them by the CHOP Data Management Core. The DSMB will report to the trial investigators within one month of the start of the DSMB meeting, or earlier if patient safety becomes an issue. Early stopping determinations will be limited to considerations of safety and adverse events; owing to the small sample size, there will be no formal early stopping for superiority or futility.

DSMB reporting: Independence of DSMB and study trial leadership

All data and the interim analyses will be conducted by the DSMB and the project statisticians, independently from the trial leadership and staff. The DSMB report will consist of the following elements:

DSMB monitoring plan and summary of report
Major protocol changes
Study accrual by month
Any violations of eligibility
Demographics
Adherence to medication
Dropout and loss of follow up
Analysis of endpoints for safety
Report of any adverse events
Formal recommendations on early stopping
Recommendations for notification to IRB

9 Data Handling and Record Keeping

9.1 Data Collection and Management

All information that is collected for this research protocol will be kept confidential. All subjects will be assigned a unique study identification number (Study ID) at the start of the protocol. This study ID will be used on all study related paperwork. Any data that is entered into an electronic format will only use the study ID. In addition, all files will be kept on a secure server or in a locked cabinet accessible only to approved study team members. A master subject list will be maintained by the study team, in a separate

password-protected file, the subject name, date of birth and unique identifier will be kept separate from all source documents. This list will be kept in a locked file cabinet.

9.2 Confidentiality

Information about study subjects will be kept confidential and managed in accordance with Institutional policies and according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.
The Investigator and study team will not use such data and records for any purpose other than conducting the study.

9.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.5 Records Retention

The investigator will retain all study essential documents for at least 3 years after study completion.

9.6 Risk Assessment

Participation in this study represents moderate risk due to the minimally invasive procedures involved and randomization of the study drug.

9.6.1 Potential risks associated with sitagliptin use

Potential risks associated with sitagliptin use are all considered rare and include hypoglycemia, hypersensitivity reactions, and pancreatitis.

Hypoglycemia is not expected with the use of sitagliptin alone because its effects on insulin secretion are glucose dependent; nonetheless, incidence of hypoglycemia will be carefully monitored by recommended twice daily glucose monitoring on a study glucometer provided to the subjects. Subjects with CFRD who may be receiving oral hypoglycemic agents or insulin therapy and performing more frequent glucose monitoring will have their oral agent or insulin doses assessed throughout their participation and adjusted as needed to avoid hypoglycemia.

Cases of serious hypersensitivity reactions in patients treated with sitagliptin have been reported in post-marketing surveillance. These reactions have included anaphylaxis, angioedema, and exfoliative skin conditions, and subjects with a history of experiencing any of these reactions will be excluded from participating in this study. Additional information from Merck that is provided in Appendix 2 indicates that reports characterized as anaphylaxis generally occurred after the first dose, which in this study will be administered under medical supervision in the Clinical & Translational Research Center. The majority of reports characterized as angioedema or skin rash were considered to be mild and non-serious. Subjects will be instructed to immediately stop their study medication and contact the Principal Investigator with the development of any rash or swelling.

Cases of acute pancreatitis have also been reported with sitagliptin use in post-marketing surveillance. Pancreatitis is not anticipated in the pancreatic insufficient CF population targeted in this study as acinar tissue is necessary for the occurrence of pancreatitis. Pancreatitis in CF begins in utero and destruction of pancreatic parenchyma is a rapid and painless process that is generally complete by infancy or early childhood (61,62). This process is in contrast to the pancreatitis that may occur in patients with pancreatic sufficient CF, which generally occurs in patients with milder mutations(63), or in subjects with chronic pancreatitis who are heterozygote or homozygote for CFTR mutations but lack sinopulmonary and other features of CF(64,65). All of the subjects participating in the present study will have classic CF with sinopulmonary disease and pancreatic insufficiency where we estimate the risk of pancreatitis to be 0. This population of CF comprises ~ 80% of both our pediatric and adult clinical practices where no cases of pancreatitis have been observed. In the remaining ~ 20% of CF patients with pancreatic sufficiency, and so excluded by design from this study, there are ~ 2 patients out of 100 experiencing an episode of pancreatitis each year. In addition to excluding from participation those CF patients with any risk for pancreatitis, subjects will also be screened and monitored for signs/symptoms and biochemical evidence of pancreatitis. The study team will review side effects after the first week and then monthly with participants. Subjects who develop abdominal pain will be instructed to stop their study medication and contact the study team for further evaluation. As specified above, serum amylase and lipase will be obtained at baseline, 4 weeks, 12 weeks, and 24 weeks. Study medication will be discontinued if pancreatitis is confirmed and appropriate management will be initiated.

In August of 2015, the U.S. Food and Drug Administration (FDA) added a new Warning and Precaution about the risk of joint pain that can be severe and disabling to the labels of all medicine in the drug class called dipeptidyl peptidase-4 (DPP-4) inhibitors. Twenty-eight cases have been reported since 2006 when sitagliptin was first approved. After the patients discontinued the DPP-4 inhibitor their symptoms were relieved, usually in less than one month. Subjects will be instructed to immediately stop their study medication and contact the Principal Investigator with the development of any new joint pain.

9.6.2 Potential risks associated with MMTT

The oral glucose tolerance test is used to annually screen for diabetes and impairments in glucose regulation in children and adults in routine clinical practice. The MMTT is a similar study but instead of administering pure glucose, a physiologic meal consisting of carbohydrates, fat and protein is consumed. Additional intermediate blood draws will be performed for glucose, insulin, GLP-1, GIP, C-peptide and glucagon. Because of these intermediate time points for blood collection, an intravenous line will be

placed, which can be associated with discomfort and a small risk of infection. The use of EMLA cream is optional to minimize discomfort to the study participant. Experienced research nurses will perform the MMTT in the outpatient CTRC facilities; MMTT are routinely performed in this setting. Eleven blood samples are required and the volumes of blood will be minimized to reduce the risk of anemia.

The major risk of the mixed meal tolerance test is hypoglycemia. Hypoglycemia is reported in 20-25% of otherwise healthy individuals who undergo oral glucose tolerance testing, the screening test recommended by the CF Foundation. Because fat and protein are ingested with the carbohydrate load during the MMTT, hypoglycemia is not anticipated. However, given the potential of abnormal incretin secretion in CF (a phenomenon observed in children with late dumping-related hypoglycemia due to fundoplication), tracking spontaneous hypoglycemia development will be important. Moreover, reactive hypoglycemia during OGTT and spontaneous hypoglycemia are reported in CF and may be related to dysregulated insulin secretion; thus tracking development of hypoglycemia in the setting of the early insulin secretory abnormalities may provide further insight into this 'spontaneous' hypoglycemia. Subjects will be closely monitored during studies by personnel with experience in managing hypoglycemia and its associated problems. Bedside glucose meters will be used to allow rapid detection and prompt treatment of hypoglycemia. Plasma or blood glucose levels will be measured (from blood drawing IV or by fingerstick) at any time during the study if symptoms of hypoglycemia occur (such as tremors, sweating, or irritability). Subjects will be treated with oral glucose supplementation (e.g. orange juice) if symptomatic.

9.6.3 Potential risks associated with GPA tests

Similar to the MMTT, the GPA test can produce reactive hypoglycemia following termination of the glucose infusion. This is unlikely in subjects with impaired glucose tolerance, and the risk is further minimized by the period glucose monitoring after the 230 mg/dl glucose clamp, and ingestion of lunch together with periodic glucose monitoring after the 340 mg/dl glucose clamp. Hypoglycemia can thus be easily averted by resuming the dextrose infusion. If plasma glucose levels decrease to ≤ 65 mg/dL, the glucose infusion will be resumed to prevent any further decrease and the development of any symptoms. All subjects will be closely monitored until blood glucose levels are stable within normal limits before discharge from the CTRC.

Intravenously administered arginine may cause a transient metallic taste in the mouth, and less often a transient sensation of warmth; allergy is rare.

9.6.4 Potential risks associated with multiple blood sampling

Blood sampling during the MMTT (65 mL), GPA test (90 mL * 2), genotyping, safety assessments and HbA1c will involve approximately 245 mL for this protocol, which is <450 ml per 6 week period recommended by the NIH. Subjects with moderate anemia (hemoglobin concentration < 10 g/dl) will be excluded from participation.

9.6.5 Other risks

Represented by this study include irritation and mild discomfort, bruising, skin infection, and mild bleeding from both the blood draws and intravenous catheters.

9.6.6 Potential Benefits of Trial Participation

Individuals with CF are living longer. Glucose abnormalities and diabetes occur in children and the prevalence steadily increases such that by age 30 y, 40-50% of adults with CF have CFRD. CFRD is associated with typical microvascular complications but more importantly worsening nutritional status, worse pulmonary function, and increased mortality. Thus, enrollment in this study is likely to improve our understanding of the mechanisms underlying insulin deficiency in CF and the role of incretin-based therapy in improving β-cell function. Participants may also enjoy meaningful indirect benefit by contributing to our understanding of insulin and incretin secretion and the risks associated with inheriting

important T2DM-risk conferring gene polymorphisms. Participants and their families may benefit from knowing that they will contribute to a clinical research study that is important to the health of individuals with CF.

9.7 Informed Consent

When a potential subject is identified, the primary CF attending will be contacted regarding the possibility of recruitment. The study team will contact the subject and review the study in full detail. These individuals will have the opportunity to ask any questions that they have.

If agreed, written informed consent will be obtained by an IRB approved member of the study team. A signed copy of the informed consent will be given to the subject. The original will be filed with the subject study files.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan in Appendix 3. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Appendix 4 for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed through Public Health Services research grant R01-DK097830 from the National Institute for Diabetes, Digestive and Kidney Diseases. The study medication (sitagliptin 100 mg tablets and matching placebo) is being provided by Merck through a non-monetary agreement.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the applicable University conflict of interest policies.

12.3 Payment to Subjects

There will be no cost to the subject for participating in this study. All procedures and supplies will be provided by the study. Following the CF-TDN (Therapeutic Development Network) guidelines for compensation of study subjects:

As the subjects are $\geq$ 18 years old, they will be compensated a total of $650.00 for time and inconvenience of participating ($150 for each of the GPA tests and $150 for the MMTT test and $25 for interim visits (Visit 3 and 4—i.e., 1 and 3 month follow up) for blood sampling.

13 Publication Plan

The investigators will present results at local and national scientific meetings. The investigators hold the primary responsibility for publication of the any results of the study.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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15 Appendices

1. Prescribing information for sitagliptin (Januvia® package insert)
2. Information requested by Dr. Rickels concerning hypersensitivity reactions identified during postapproval use of sitagliptin
3. Data and Safety Monitoring Plan
4. Informed Consent Form
5. Subject's Medication Guide